



U.S. Application No.

Unknown

Date: April 26, 2001



International Application No.

PCT/US98/13071

04-ZT-01  
JN17 Rec'd PCT/PTO 26 APR 2001  
\$

Attorney Docket No.

STERN1.001APC

09/830703 Page 1

**TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 USC 371**

International Application No.: PCT/EP00/08071

International Filing Date: August 18, 2000

Priority Date Claimed: August 30, 1999

Title of Invention: TRANSGENIC ANIMAL MODEL FOR NEURODEGENERATIVE  
DISEASES

Applicant(s) for DO/EO/US: Lübbert, Hermann

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1.  This is a **FIRST** submission of items concerning a filing under 35 USC 371.
2.  This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 USC 371.
3.  This express request to begin national examination procedures (35 USC 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 USC 371(b) and PCT Articles 22 and 39(1).
4.  A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5.  A copy of the International Application as filed (35 USC 371(c)(2))
  - a)  is transmitted herewith (required only if not transmitted by the International Bureau).
  - b)  has been transmitted by the International Bureau.
  - c)  is not required, as the application was filed in the United States Receiving Office (RO/US).
6.  A translation of the International Application into English (35 USC 371(c)(2)).
7.  Amendments to the claims of the International Application under PCT Article 19 (35 USC 371(c)(3))
  - a)  are transmitted herewith (required only if not transmitted by the International Bureau).
  - b)  have been transmitted by the International Bureau.
  - c)  have not been made; however, the time limit for making such amendments has NOT expired.
  - d)  have not been made and will not be made.
8.  A translation of the amendments to the claims under PCT Article 19 (35 USC 371(c)(3)).
9.  An oath or declaration of the inventor(s) (35 USC 371(c)(4)).
10.  A copy of the International Preliminary Examination Report with any annexes thereto, such as any amendments made under PCT Article 34.
11.  A translation of the annexes, such as any amendments made under PCT Article 34, to the International Preliminary Examination Report under PCT Article 36 (35 USC 371(c)(5)).

09/830703

Attorney Docket No.

STERN1.001APC

JC08 Rec'd PCT/PTO

26 APR 2001  
Page 2U.S. Application No.  
Unknown'International Application No.  
PCT/US98/13071

Date: April 26, 2001

12.  An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

13.  An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

14.  A FIRST preliminary amendment.  
 A SECOND or SUBSEQUENT preliminary amendment.

15.  International Application as published.

16.  This applicant qualifies for small entity status.

17.  PCT Form PCT/IPEA/402.

18.  PCT Form PCT/IB/308.

19.  PCT request form.

20.  Other Items or information:  
1. International Search Report  
2. Notification of the International Application Number and of the International Filing Date

21.  A return prepaid postcard.

22.  The following fees are submitted:

**FEES**

| <b>BASIC FEE</b>   |                     |                     | \$860       |      |
|--|---------------------|---------------------|-------------|------|
| <b>CLAIMS</b>  | <b>NUMBER FILED</b> | <b>NUMBER EXTRA</b> | <b>RATE</b> |      |
| Total Claims   | 24 - 20 =           | 4 ×                 | \$18        | \$72 |
| Independent Claims   | 2 - 3 =             | 0 ×                 | \$80        | \$0  |
| Multiple dependent claims(s) (if applicable)   |                     |                     | \$270       | \$0  |
| <b>TOTAL OF ABOVE CALCULATIONS</b>   |                     |                     | \$          | 932  |
| Reduction by 1/2 for filing by small entity (if applicable). Verified Small Entity statement must also be filed. (NOTE 37 CFR 1.9, 1.27, 1.28) |                     |                     | \$          | -466 |
| <b>TOTAL NATIONAL FEE</b>  |                     |                     | \$          | 466  |
| <b>TOTAL FEES ENCLOSED</b>   |                     |                     | \$          | 466  |
| amount to be refunded:   |                     |                     | \$          |      |
| amount to be charged:  |                     |                     | \$          |      |

09/830703

Attorney Docket No.

STERN1.001APC

JC08 Rec'd PCT/PTO

26 APR 2001

Page 3

U.S. Application No.  
Unknown

International Application No.  
PCT/US98/13071

Date: April 26, 2001

23.  The fee for submission of the translation of the international application or any annexes to the IPER set forth in 37 CFR 1.492(f) will be paid upon submission of those items.

24.  The fee for later submission of the signed oath or declaration set forth in 37 CFR 1.492(e) will be paid upon submission of the declaration.

25.  A check in the amount of \$466 to cover the above fees is enclosed.

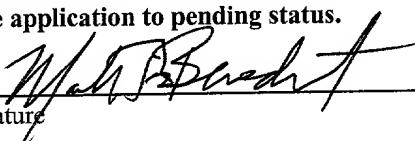
26.  A check in the amount of \$40 to cover the fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40 per property.

27.  The Commissioner is hereby authorized to charge only those additional fees which may be required, now or in the future, to avoid abandonment of the application, or credit any overpayment to Deposit Account No. 11-1410. A duplicate copy of this sheet is enclosed.

**NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.**

SEND ALL CORRESPONDENCE TO:

KNOBBE, MARTENS, OLSON & BEAR, LLP  
620 Newport Center Drive  
Sixteenth Floor  
Newport Beach, CA 92660

  
\_\_\_\_\_  
Signature

\_\_\_\_\_  
Mark R. Benedict  
Printed Name

\_\_\_\_\_  
44,531  
Registration Number

O:\DOCS\JYH\JYH-1260.DOC:vb /is  
042601



STERN1.001.APC

PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

SUPPLEMENTAL PRELIMINARY AMENDMENT

Assistant Commissioner for Patents  
Washington, D.C. 20231

Dear Sir:

Prior to examination on the merits and subsequent to the Preliminary Amendment mailed April 26, 2001, please amend the above-captioned application as follows:

## IN THE SPECIFICATION

Please replace the word “more” with --less-- on page 9, line 17.

IN THE CLAIMS

Please amend Claim 1 as follows:

1. (Twice Amended) An isolated or purified polynucleotide encoding a mouse parkin2 protein, containing mutations or deletions in at least one of the exons 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, or 12, or containing a frame-shift mutation in exon 4, wherein said mutation causes Parkinson's disease.

**REMARKS**

The amendment to the specification (page 9) was made to correct an inadvertent error introduced by the Preliminary Amendment of April 26, 2001. The amendment to Claim 1 was

Appl. No. : 09/830,703  
Filed : April 26, 2001

made in order to more distinctly claim the present invention. Support for the amendment to Claim 1 may be found in Tables 1 and 2, on pages 18 and 19, respectively, as well as on page 8 lines 17-19 of the specification. The specific amendments to the application are shown on a separate set of pages attached hereto and entitled **VERSION WITH MARKINGS TO SHOW CHANGES MADE**, which follows the signature page of this Amendment. On this set of pages, the insertions and [deletions] are indicated.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410. A duplicate copy of this sheet is enclosed.

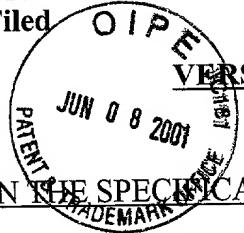
Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 6/5/01

By: Mark R. Benedict  
Mark R. Benedict  
Registration No. 44,531  
Attorney of Record  
620 Newport Center Drive  
Sixteenth Floor  
Newport Beach, CA 92660

Appl. No. : 09/830,703  
Filed : April 26, 2001



VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The paragraph beginning on page 9, line 12, has been deleted and rewritten as follows:

To obtain at least a transgenic non-human animal as a model for neurodegenerative diseases, the natural occurring sequence of the parkin gene in this animal may be replaced on one or both alleles of the chromosomes by a sequence of mPark2, containing mutations or deletions according to the present invention. These animals produce either less or [more] less active or no parkin protein.

IN THE CLAIMS:

1. (Twice Amended) An isolated or purified polynucleotide encoding a [mutant] mouse parkin2 protein, or a homolog thereof, containing mutations or deletions in at least one of the exons 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, or 12, or containing a frame-shift mutation in exon 4, wherein said [mutant] mutation causes Parkinson's disease.

O:\DOCS\CMS\CMS-1340.DOC  
053001

09/830703

JC08 Rec'd PCT/PTO 26 APR 2007  
PATENT

STERN1.001APC

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

|           |   |                   |                          |
|-----------|---|-------------------|--------------------------|
| Applicant | : | Lubbert et al.    | ) Group Art Unit Unknown |
|           |   |                   | )                        |
| Appl. No. | : | Unknown           | )                        |
|           |   |                   | )                        |
| Filed     | : | Herewith          | )                        |
|           |   |                   | )                        |
| For       | : | TRANSGENIC ANIMAL | )                        |
|           |   | MODEL FOR         | )                        |
|           |   | NEURODEGENERATIVE | )                        |
|           |   | DISEASES          | )                        |
|           |   |                   | )                        |
| Examiner  | : | Unknown           | )                        |

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents  
Washington, D.C. 20231

Dear Sir:

Preliminary to examination on the merits, please amend the above-captioned U.S. national phase application as follows:

**IN THE SPECIFICATION:**

Please insert the following paragraph and heading, immediately following the title, as follows:

--Cross-Reference to Related Applications

This is the U.S. National Phase under 35 U.S.C. § 371 of International Application Number PCT/EP00/08071, filed August 18, 2000 which claims priority to European Application Number 99116766.9, filed August 30, 1999 under 35 U.S.C. § 119, the disclosures of which are incorporated herein by reference.--

Please insert the following heading, immediately following the "Cross-Reference to Related Applications":

--Field of the Invention--

Appl. No. : Unknown  
Filed : Herewith

Please replace the paragraph beginning on page 1, line 3, with the following rewritten paragraph:

--This invention relates to a transgenic animal model containing mutated mouse parkin2 DNA and translated protein sequence. The use of a transgenic animal can be used as a model for neurodegenerative diseases, preferably Parkinson's disease.--

Please insert the following heading prior to the paragraph beginning at page 1, line 13:

--Description of the Related Art--

Please replace the word "insults" found on page 1, line 18, with the word --insights--.

Please insert --(PD)-- immediately following "Parkinson's Disease" found on page 2, line 8.

Please insert prior to the paragraph beginning at page 4, line 9, the following heading and paragraph:

--Summary of the Invention--

Please insert the paragraph beginning at page 1, line 3.

Following the "Summary of the Invention" and paragraph, please insert the following heading and paragraph:

--Brief Description of the Drawings--

Please insert the paragraphs beginning at page 25, line 28 and ending at page 26, line 15.

Following the "Brief Description of the Drawings" and inserted paragraphs, please insert the following heading:

--Description of the Preferred Embodiment--

Please replace the word "analysing" found on page 5, line 18, with the word --analyzing--.

Please delete the end of the sentence beginning at page 5, line 17, starting with the word "...whereby it is..."

Please replace the word "content" with --context of-- found on page 7, line 19.

Please replace the word "ore" with --or-- found on page 8, line 2.

Please replace the word "less" with --more-- found on page 9, line 17.

Please delete the word "Briefly" found on page 9, line 28 and begin the sentence with "A vector is..."

Please insert the word --If-- prior to "The vector is..." on page 10, line 1.

Please replace the word "and" with --it-- on page 10, line 1.

**Appl. No.** : **Unknown**  
**Filed** : **Herewith**

Please replace the word "expiration" with --expression vector-- found on page 16, line 2.

Please replace the words "The pups will usually be..." with --Offspring are generally...-- found on page 20, line 17.

Please insert the word --are-- on page 22, line 12 after the word "Preferred."

Please insert the word --that-- on page 22, line 14 after the word "lines."

Please delete the paragraph beginning at page 26, line 7.

**IN THE CLAIMS:**

**Please cancel the following claims:** 2, 9, 10, 11, 12, 16, 19, 21

**Please amend the remaining claims as follows:**

1. (Amended) An isolated or purified polynucleotide encoding a mutant mouse parkin2 protein, or a homolog thereof, wherein said mutant causes symptoms of Parkinson's disease.

3. (Amended) The polynucleotide of claim 1, wherein said polynucleotide is selected from the group consisting of: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO: 9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, and SEQ ID NO:20.

4. (Amended) A vector, comprising the polynucleotide of claim 1.

5. (Amended) A cell, comprising the polynucleotide of claim 1.

6. (Amended) The cell of claim 5, wherein the cell is a prokaryotic or a eukaryotic cell.

7. (Amended) A parkin mouse protein, comprising any amino acid sequence selected from the group consisting of: SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, and SEQ ID NO:34.

8. (Amended) A transgenic non-human mammal comprising the isolated or purified polynucleotide of claim 1.

13. (Amended) A mammalian cell-line transformed or transfected with the polynucleotide of claim 1.

14. (Amended) A method of producing a transgenic animal, comprising:

**Appl. No.** : **Unknown**  
**Filed** : **Herewith**

constructing a vector that carries the polynucleotide of claim 1;  
introducing said vector into embryonic stem cells;  
injecting said embryonic stem cells into blastocysts; and  
placing said blastocysts into a pseudopregnant female animal.

15. (Amended) A mammalian model for a neurodegenerative disease comprising the transgenic mammal of claim 8.

17. (Amended) A method for testing the efficacy of a treatment for a neurodegenerative disease, comprising:

subjecting the mammalian model of claim 15 to a putative treatment or agent; and  
determining the efficacy of said treatment by identifying a reduction in the  
symptoms of said neurodegenerative disease.

18. (Amended) The method of claim 17, wherein said neurodegenerative disease is selected from the group consisting of: Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, Multisystem atrophy, Wilson's disease, Pick's disease, and Prion disease.

20. (Amended) A method for testing whether an active substance is useful for treating the symptoms of Parkinson's disease comprising:

administering said active substance to the transgenic animal of claim 8; and  
determining whether said active substance reduces the symptoms of Parkinson's disease.

22. (Amended) A descendant of the transgenic animal according to claim 8, wherein said animal is obtained by breeding with the same or any other genotype.

**Please add the following claims:**

23. (New) The polynucleotide of claim 1, wherein said mutant comprises a point mutation, deletion or fragment.

24. (New) The polynucleotide of claim 1, wherein said homolog is human.

25. (New) The cell of claim 5, wherein said eukaryotic cell is a fungal, insect or mammalian cell.

26. (New) The cell of claim 25, wherein said fungal cell is a yeast cell.

Appl. No. : Unknown  
Filed : Herewith

27. (New) The cell of claim 25, wherein said prokaryotic cell is a bacterial cell.

28. (New) The polynucleotide of claim 1, wherein said mutants comprise mutations in exon 1 or exon 3.

29. (New) The mammalian model of claim 15, wherein said animal is a mouse or rat.

30. (New) A method of testing agents for efficacy and toxicity in treating a neurodegenerative disease, comprising:

administering said agent to the mammalian model of claim 15; and

identifying whether said agent reduces the symptoms of said neurodegenerative disease or is toxic to said mammal.

31. (New) A method for testing whether an active substance is useful for treating the symptoms of Parkinson's disease, comprising:

administering said active substance to the cell-line of claim 13; and

determining whether said active substance reduces the symptoms of Parkinson's disease.

32. (New) The method of claim 20, further comprising testing various dosages of said active substance.

#### REMARKS

The foregoing amendments more closely conform the application to U.S. practice. The above requested changes to the application do not add new matter, and entry of the amendments is respectfully requested.

The specific changes to the specification are shown on a separate set of pages attached hereto and entitled VERSION WITH MARKINGS TO SHOW CHANGES MADE, which follows the signature page of this amendment. On this set of pages, the insertions are underlined while [brackets denote deletions].

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410. A duplicate copy of this sheet is enclosed.

Appl. No. : **Unknown**  
Filed : **Herewith**

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 4/26/01

By: Mark R. Benedict

Mark R. Benedict  
Registration No. 44,531  
Attorney of Record  
620 Newport Center Drive  
Sixteenth Floor  
Newport Beach, CA 92660

O:\DOCS\JYH\JYH-1241.DOC  
032701

Appl. No. : Unknown  
Filed : Herewith

**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**IN THE SPECIFICATION:**

The following paragraph and heading has been added, immediately following the title:

**Cross-Reference to Related Applications**

This is the U.S. national phase under 35 U.S.C. § 371 of International Application Number PCT/EP00/08071, filed August 18, 2000 which claims priority to European Application Number 99116766.9, filed August 30, 1999 under 35 U.S.C. § 119, the disclosures of which are incorporated herein by reference.

The following heading has been added following the section entitled "Cross-Reference to Related Applications":

**Field of the Invention**

The paragraph beginning on page 1, line 3, has been deleted and rewritten as follows:

[The present invention relates to a mouse parkin2 DNA- and protein sequence containing naturally occurring or artificially introduced mutations or deletions, which cause Parkinson's disease in a human if they occur in the according human sequence, the construction of a truncated parkin gene, which expresses no, a non-active or a truncated parkin protein and a model of a transgenic animal, expressing such a less or non-active parkin protein instead of the native parkin protein or no parkin protein, as well as to the use of such a transgenic animal as a model for neurodegenerative diseases, preferred Parkinson's disease.] This invention relates to a transgenic animal model containing mutated mouse parkin2 DNA and translated protein sequence. The use of a transgenic animal can be used as a model for neurodegenerative diseases, preferably Parkinson's disease.

The following heading has been added prior to the paragraph beginning at page 1, line 13:

**Description of the Related Art**

The paragraph beginning at page 1, line 13 has been amended as follows:

Neurodegenerative disorders are some of the most feared illnesses in society. During the last 10 years some of the genetic causes of many of the primary neurodegenerative disorders like Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, prion disease and several ataxic syndromes, have been identified. These findings gave new [insults] insights in the knowledge about the initiating trigger as well as the resulting

Appl. No. : Unknown  
Filed : Herewith

consequences of those diseases. Due to the fact that these diseases have many pathological mechanisms in common it seems possible that only relatively few pathways to neuronal death are involved in these disorders. Thus, treatment strategies for a particular neurodegenerative disease may be found to have value in other related disorders.

The paragraph beginning on page 2, line 8, has been amended as follows:

In both the early and late onset types of Parkinson's disease (PD), the pathology is the same but the abnormalities tend to be more severe and more widespread in cases beginning at an earlier age. The disease is characterised by lesions in brain areas where the cell bodies of the dopaminergic neurons are located mainly in the substantia nigra compacta. In addition intracytoplasmic inclusions known as Lewy bodies can be observed in different brain regions, in particular in substantia nigra and the locus ceruleus.

The following heading and paragraph has been added prior to the paragraph beginning at page 4, line 9 as follows:

#### Summary of the Invention

The present invention relates to a mouse parkin2 DNA- and protein sequence containing naturally occurring or artificially introduced mutations or deletions, which cause Parkinson's disease in a human if they occur in the according human sequence, the construction of a truncated parkin gene, which expresses no, a non-active or a truncated parkin protein and a model of a transgenic animal, expressing such a less or non-active parkin protein instead of the native parkin protein or no parkin protein, as well as to the use of such a transgenic animal as a model for neurodegenerative diseases, preferred Parkinson's disease.

The following heading and paragraph have been added following the section entitled "Summary of the Invention":

#### Brief Description of the Invention

Figure 1 shows the alignment of the deduced amino acid sequences of the human and mouse Parkin2 protein (SEQ ID NO: 4).

Underlined are the conserved ubiquitin like (at the N-terminus) and Ring finger like (at the C-terminus) regions of both proteins.

Figure 2 shows the alignment of the nucleotide sequences of the human and mouse parkin 2 gene. Bold lines represent the exon boundaries identified for the human and mouse sequence.

Appl. No. : Unknown  
Filed : Herewith

Figure 3 represents a flow chart of the cloning procedure of the mouse parkin2 gene - exon3 knock-out construct.

The following heading has been added following the section entitled "Brief Description of the Invention."

Description of the Drawings

The paragraph beginning at page 5, line 17, has been amended as follows:

The transgenic non-human animals according to the present invention can be used as models for [analysing] analyzing the symptoms of neurodegenerative diseases or as a model system for testing the efficacy of a treatment for a neurodegenerative disease[, whereby it is not an object of the present application to provide any method for treating one of the described diseases in a human or animal].

The paragraph beginning at page 7, line 19, has been amended as follows:

"Homologous amino acid sequence" in [content] context of with the mouse parkin2 protein means in the present application an amino acid sequence, wherein at least 70 %, preferably 80 %, more preferably 90 % of the amino acids are identical to one of the proteins of the present invention and wherein the replaced amino acids preferably are replaced by homologous amino acids. As "homologous" amino acids are designated which have similar features concerning hydrophobicity, charge, steric features etc. Most preferred are amino acid sequences, containing the species-dependent differences of the mouse amino acid sequence compared to human parkin protein shown in the alignment Figure No. 1. The alignment of the corresponding polynucleotide sequences with the exon boundaries is shown in Figure No. 2.

The paragraph beginning at page 8, line 2, has been amended as follows:

In the whole application for nucleotides and amino acids the usual designations (one-letter [ore] or three-letter code) are used, known by any person skilled in the art.

The paragraph beginning at page 9, line 17 has been amended as follows:

To obtain at least a transgenic non-human animal as a model for neurodegenerative diseases, the natural occurring sequence of the parkin gene in this animal may be replaced on one or both alleles of the chromosomes by a sequence of mPark2, containing mutations or deletions according to the present invention. These animals produce either less or [less] more active or no parkin protein.

The paragraph beginning at page 9, line 28, has been amended as follows:

**Appl. No.** : **Unknown**  
**Filed** : **Herewith**

[Briefly, a] A vector is constructed that carries the replacement DNA. Both ends of the replacement DNA are flanked by long DNA sequences homologous to the sequences flanking the target DNA. When the vector is introduced into ES cells, the homologous sequences align and recombination may take place. This results in the target DNA being exchanged for the replacement DNA. If the [The] vector is not replicated in the cells, it [and] will be lost. The frequency of homologous recombination is low; thus, a screening system is used. The replacement DNA will contain a positive marker sequence, usually a neomycin resistance gene. Thus, any cells that incorporate the replacement DNA by homologous recombination will resist neomycin. By growing cells in medium containing the drug neomycin one can select only those cells containing the replacement DNA. The ES cells containing the replacement DNA are then inserted into recipient mouse blastocysts to create chimeric mice. Chimeras with germ cells derived for the altered ES cells transmit the modified genome to their offspring, yielding mice heterozygous for the target DNA (contain one target DNA and one replacement DNA). The heterozygotes are then bred with each other either to create mice homozygous for the replacement DNA and deficient in the target DNA or to maintain transgenic heterozygotes if the homozygotic mice are not viable.

The paragraph beginning on page 16, line 1, has been amended as follows:

Further to the above described techniques a step of expressing the treated sequence may be inserted in the [expiration] expression vector. Therefore the construct is (sub)cloned into any expression vector, which may be brought into a suitable eukaryotic cell. These expression vectors are typically replicable in the host organisms either as episomes or as an integral part of the host chromosomal DNA. Commonly, expression vectors will contain selection markers, e.g., tetracycline resistance or hygromycin resistance, to permit detection and/or selection of those cells transformed with the desired DNA sequences. Polynucleotides encoding a variant parkin2 polypeptide may include sequences that facilitate transcription (expression sequences) and translation of the coding sequences, such that the encoded polypeptide product is produced. Construction of such polynucleotides is well known in the art and is described further in Maniatis et al. Molecular Cloning: A Laboratory Manual, 2nd Ed. (1989), Cold Spring Harbor, N.Y. For example, but not for limitation, such polynucleotides can include a promoter, a transcription termination site (polyadenylation site in eukaryotic expression hosts), a ribosome binding site,

Appl. No. : Unknown  
Filed : Herewith

and, optionally, an enhancer for use in eukaryotic expression hosts, and, optionally, sequences necessary for replication of a vector.

The paragraph beginning on page 20, line 17, has been amended as follows:

[The pups will usually be] Offspring are generally born 16-18 days after introduction of the blastocysts into foster mothers. Chimeric animals will be mated with wild type (wt) mice to create heterozygote transgenics.

The paragraph beginning on page 22, line 12, has been amended as follows:

Preferred are the above described polynucleotide sequences, the proteins and amino acid sequences as well as the transgenic animal models and cell lines that may be used for any method for analysing the symptoms of neurodegenerative diseases.

The paragraph beginning on page 26, line 8, has been deleted:

[a) Restriction endonucleases:

N = NotI, E= Eco RI, B= BamHI, H= HindIII, X= XbaI.

b) Modifications: ()= T4 DNA polymerase treatment in order to remove a restriction site in the resulting plasmid.

c)  =pBluescript KSII (Stratagene) vector sequence  
 = λ-Fix vector sequence

d) HSV-tk = herpes simples promotor and thymidine kinase gene

e) kb = kilobases]

#### IN THE CLAIMS:

Claims 2, 9, 10, 11, 12, 16, 19, 21 have been deleted.

The remaining claims have been amended as follows.

1. (Amended) [A] An isolated or purified polynucleotide [sequence] encoding a mutant mouse parkin2 protein, or a homolog thereof, wherein said mutant causes [containing naturally occurring or artificially introduced mutations or deletions, which cause] Parkinson's disease [in a human if they occur in the according human sequence].

3. (Amended) The [sequence] polynucleotide of claim 1 [or 2], wherein [the sequence] said polynucleotide is selected from the group[,] consisting of: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:7 SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ

Appl. No. : Unknown  
Filed : Herewith

ID NO:18, and SEQ ID NO:19, SEQ ID NO:20 [**or naturally occurring or artificially introduced mutants or fragments thereof**].

4. (Amended) A vector, [containing any sequence according to any]  
comprising the polynucleotide of [claims] claim 1 [to 3].

5. (Amended) A [prokaryotic or eukaryotic] cell, [containing a vector  
according to] comprising the polynucleotide of claim [4] 1.

6. (Amended) The cell of claim 5, [characterised in that] wherein the cell is  
[selected from bacterial or yeast cells, insect cells or mammalian cells as primary cells or  
immortalised cell lines]a prokaryotic or eukaryotic cell.

7. (Amended) A parkin mouse protein, comprising any [with an] amino acid  
sequence selected from the group consisting of: SEQ ID NO:5, SEQ ID NO:6 SEQ, ID NO:21,  
SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID  
NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ  
ID NO:33, and SEQ ID NO:34 [**or naturally occurring or artificially introduced mutants with a**  
**homologous protein sequence or fragments thereof**].

8. (Amended) A transgenic non-human [animal] mammal[,] comprising the  
isolated or purified polynucleotide of claim 1 [whose one or both alleles of a gene encoding a  
parkin gene are mutated or truncated in a way, that a protein with modified, preferred less  
activity or no active protein is expressed].

13. (Amended) A mammalian cell-line transformed or transfected with the  
polynucleotide of claim 1[any sequence according to any of claims 1 to 3 or a vector  
according to claim 4 or cell lines or primary cultures derived from the transgenic animal of  
any of claims 8 to 12].

14. (Amended) A method of producing a transgenic animal, comprising:  
[according to any of claims 8 to 12 or a cell line according to claim 13.]  
constructing a vector that carries the polynucleotide of claim 1;  
introducing said vector into embryonic stem cells;  
injecting said embryonic stem cells into blastocysts; and  
placing said blastocysts into pseudopregnant female animal.

Appl. No. : Unknown  
Filed : Herewith

15. (Amended) [Use of the transgenic non-human animal according to any of claims 8 to 12 or a cell line according to claim 13 as a] A mammalian model for a neurodegenerative [diseases] disease comprising the transgenic mammal of claim 8.

17. (Amended) A method for testing the efficacy of a treatment for a neurodegenerative disease, comprising: [associated with a less active or non-active parkin protein, comprising subjecting any model of claim 15 to a putative treatment and determining the efficacy of said treatment.]

subjecting the mammalian model of claim 15 to a putative treatment or agent; and determining the efficacy of said treatment by identifying a reduction in the symptoms of said neurodegenerative disease.

18. (Amended) The method [according to] of claim [16 or] 17, wherein said neurodegenerative disease is selected from the group consisting of: Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, Multisystem atrophy, Wilson's disease, Pick's disease, and Prion disease[, or second causes inducing Parkinson's syndromes like toxins, drugs, brain tumors, head trauma, stroke, vascular irregularities, or metabolic irregularities].

20. (Amended) [Use of any model according to claim 15] A method for testing whether an active substance is useful for treating the symptoms of Parkinson's disease comprising: [a condition associated with non-active parkin protein comprising administering said active substance to the transgenic animal of any of claims 8 to 12 or a cell-line of claim 13, and determining a level of the active substance, which causes an effect in treating the disease.]

administering said active substance to the transgenic animal of claim 8, and determining whether said active substance reduces the symptoms of Parkinson's disease.

22. (Amended) A descendant [Descendant] of the transgenic animal according to [any of claims] claim 8 [to 12] wherein, said animal is obtained by breeding with the same or any other genotype.

**The following claims have been added.**

23. (New) The polynucleotide of claim 1, wherein said mutant comprises a point mutation, deletion or fragment.

**Appl. No.** : **Unknown**  
**Filed** : **Herewith**

24. (New) The polynucleotide of claim 1, wherein said homolog is human.

25. (New) The cell of claim 5, wherein said eukaryotic cell is a fungal, insect or mammalian cell.

26. (New) The cell of claim 25, wherein said fungal cell is a yeast cell.

27. (New) The cell of claim 25, wherein said prokaryotic cell is a bacterial cell.

28. (New) The polynucleotide of claim 1, wherein said mutants comprise mutations in exon 1 or exon 3.

29. (New) The mammalian model of claim 15, wherein said animal is a mouse or rat.

30. (New) A method of testing agents for efficacy and toxicity in treating a neurodegenerative disease, comprising:  
administering said agent to the mammalian model of claim 15; and  
identifying whether said agent reduces the symptoms of said neurodegenerative disease or is toxic to said mammal.

31. (New) A method for testing whether an active substance is useful for treating the symptoms of Parkinson's disease, comprising:  
administering said active substance to the cell-line of claim 13; and  
determining whether said active substance reduces the symptoms of Parkinson's disease.

32. (New) The method of claim 20, further comprising testing various dosages of said active substance.

Transgenic animal model for neurodegenerative diseases

The present invention relates to a mouse parkin2 DNA- and protein sequence containing naturally occurring or artificially introduced mutations or 5 deletions, which cause Parkinson's disease in a human if they occur in the according human sequence, the construction of a truncated parkin gene, which expresses no, a non-active or a truncated parkin protein and a model of a transgenic animal, expressing such a less or non-active parkin protein instead of the native parkin protein or no parkin protein, as well 10 as to the use of such a transgenic animal as a model for neurodegenerative diseases, preferred Parkinson's disease.

Neurodegenerative disorders are some of the most feared illnesses in society. During the last 10 years some of the genetic causes of many of 15 the primary neurodegenerative disorders like Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, prion disease and several ataxic syndromes, have been identified. These findings gave new insights in the knowledge about the initiating trigger as well as the resulting consequences of those diseases. Due to the fact that 20 these diseases have many pathological mechanisms in common it seems possible that only relatively few pathways to neuronal death are involved in these disorders. Thus, treatment strategies for a particular neurodegenerative disease may be found to have value in other related disorders.

25

Parkinson's disease is a progressive neurodegenerative movement disorder with severe symptoms like rigidity, bradykinesia or tremor. The disease symptoms appear after degeneration of more than 70-80% of dopaminergic neurons. Broadly speaking the disease falls into two categories, namely 30 late onset and early onset. Late onset, which occurs in older age (55+ years), mainly as consequence of environmental influences, leads to

enhanced dopaminergic neuron death at a faster rate and to a more severe degree than normal. Early onset Parkinson's disease is much more infrequent but starts between the ages of 35 and 60 years. There is evidence that three forms of this early type of Parkinson's disease show a 5 tendency to run in families and is therefore known as familial Parkinson's disease.

In both the early and late onset types of Parkinson's disease, the pathology is the same but the abnormalities tend to be more severe and 10 more widespread in cases beginning at an earlier age. The disease is characterised by lesions in brain areas where the cell bodies of the dopaminergic neurons are located mainly in the substantia nigra compacta. In addition intracytoplasmic inclusions known as Lewy bodies can be observed in different brain regions, in particular in substantia nigra and 15 the locus ceruleus.

Recently two loci could be identified associated with early onset PD, one on human chromosome 4q21-23 ("PARK 1" gene locus) with a gene defect to be due to a missense mutation in the  $\alpha$ -synuclein protein (or *parkin1*), a 20 small abundant brain molecule (Polymeropoulos, M. et al., Science 1997; 276:2045-2047), and one on chromosome 2p13 ("PARK 3" gene locus)(Gasser, T. et al.. Nat. Genet. 1998; 18: 262-265). Both forms are inherited in an autosomal dominant manner.

25 Lately an autosomal recessive form of familial Parkinson's disease could be observed, linked to human chromosome 6q25.2-27 ("PARK 2" gene locus) (Matsumine, H. et al., Am J Hum Genet (1997); 60: 588-596). This gene, designated *parkin* (or later *parkin2*) contains 12 exons spanning more than 500 kb and encodes a protein of 465 amino acids (molecular weight 51,652 30 Dalton) with homology to ubiquitin at the N-terminal portion and a RING-finger like motif at the C-terminal portion.

It has been shown, that mutations in the  $\alpha$ -synuclein gene lead to autosomal dominant Parkinson's disease (Polymeropoulos, M.. et al., Science 1997; 276: 2045-2047), as well as mutations in the parkin gene cause autosomal recessive juvenile parkinsonism (Kitada, T. et al., Nature 1998; 392: 605-608; Hattori, N. et al., Biochem Biophys Res Comm 1998; 249: 754-758)).

Further Hattori, N. et al., have been shown in Ann Neurol 1998; 44: 935-941, that different deletions in the parkin gene are the reason for 10 truncated parkin proteins, causing autosomal recessive juvenile parkinsonism. Especially intragenic deletional mutations, involving exons 3 to 4, exon 3, exon 4 and exon 5, as well as exon 3 through exon 7 are described as effecting the disease. Deletion of exon 3 of the parkin gene is furthermore described by Lücking, C. et al. in the Lancet 1998; 352: 15 1355-1356 to cause autosomal recessive juvenile parkinsonism.

Investigations of Abbas, N. et al. Human Molecular Genetics 1999; 8: 567-574 and Kitada, T. et al., Nature 1998; 392: 805-808 show that mutations in the ubiquitin-like N-terminal part (exon 2) of the parkin gene can also cause autosomal recessive juvenile parkinsonism, as well as different 20 frameshift- or missense mutations.

Leroy, E. et al., demonstrated in Hum Genet 1998; 103: 424-427 that 25 deletions of exons 5, 6 and 7 of the human parkin gene leads to early onset Parkinson's disease.

At present most common therapies are dealing with the increase of dopamine content in PD patients via application of L-dopa as precursor of dopamine, dopamine agonists or MAO-B (Monoamino Oxidase B) inhibitors, e.g. Deprenyl, by blocking the degradation of dopamine. There are no prophylactic 30 therapies available to stop the progression of the degenerative disease before onset of symptoms in late onset PD. This is due to the fact that at present diagnosis is only possible when first symptoms occur. So

far it is not clear to which extent genetic components enhance the environmental components responsible for the increased cell death of dopaminergic neurons.

5 Although different transgenic animal models for neurodegenerative diseases like Alzheimer's disease have been created, a transgenic animal model for Parkinson's disease has not yet been described.

Homologous recombination may be employed for inactivation or alteration of genes in a site-directed manner. A number of papers describe the use of homologous recombination in mammalian cells, including human cells. Illustrative of these papers are Kucherlapati *et al.* (1984) Proc. Natl. Acad. Sci. USA 81:3153-3157; Kucherlapati *et al.* (1985) Mol. Cell. Bio. 5:714-720; Smithies *et al.* (1985) Nature 317:230-234; Wake *et al.* (1985) Mol. Cell. Bio. 8:2080-2089; Ayares *et al.* (1985) Genetics 111:375-388; Ayares *et al.* (1986) Mol. Cell. Bio. 7:1656-1662; Song *et al.* (1987) Proc. Natl. Acad. Sci. USA 84:6820-6824; Thomas *et al.* (1986) Cell 44:419-428; Thomas and Capecchi (1987) Cell 51:503-512; Nandi *et al.* (1988) Proc. Natl. Acad. Sci. USA 85:3845-3849; and Mansour *et al.* (1988) Nature 336:348-352. Various aspects of using homologous recombination to create specific genetic mutations in embryonic stem cells and to transfer these mutations to the germline have been described (Evans and Kaufman (1981) Nature 294:154-146; Dotschman *et al.*, (1987) Nature 330:576-578; Thomas and Capecchi (1987) Cell 51:503-512; Thompson *et al.* (1989) Cell 56:316-25 321. The combination of a mutant polyoma enhancer and a thymidine kinase promoter to drive the neomycin gene has been shown to be active in both embryonic stem cells and EC cells by Thomas and Capecchi, *supra*, 1987; Nicholas and Berg (1983) in Teratocarcinoma Stem Cell, eds. Siver, Martin and Strikland (Cold Spring Harbor Lab., Cold Spring Harbor, N.Y. (pp. 469-30 497); and Linney and Donerly, Cell 35:693-699, 1983.

The object of the present application is to provide the suppositions for a test model for neurodegenerative diseases, preferably Parkinson's disease and a valuable tool in the diagnosis and treatment of these conditions, as well as the development of experimental models of Parkinson's disease that  
5 can be used to define further the underlying biochemical events involved in the pathogenesis of this disease.

This object is met by a polynucleotide sequence encoding a mouse parkin2 protein, containing naturally occurring or artificially introduced  
10 mutations or deletions, which cause Parkinson's disease in a human if they occur in the according human sequence, a vector, containing such a sequence, a prokaryotic or eukaryotic cell, containing such a vector and a transgenic non-human animal, whose one or both alleles of a gene encoding a parkin gene are mutated in a way, that a protein with modified,  
15 preferred less activity or no active protein is expressed.

The transgenic non-human animals according to the present invention can be used as models for analysing the symptoms of neurodegenerative diseases or as a model system for testing the efficacy of a treatment for a neuro-degenerative disease, whereby it is not an object of the present  
20 application to provide any method for treating one of the described diseases in a human or animal.

Such models could presumably be employed, in one application, to screen  
25 for agents that alter the degenerative course of Parkinson's disease. For example, a model system of Parkinson's disease could be used to screen for environmental factors that induce or accelerate the pathogenesis. Further an experimental model could be used to screen for agents that inhibit, prevent, or reverse the progression of Parkinson's disease. Presumably,  
30 such models could be employed to develop pharmaceuticals that are effective in preventing, arresting, or reversing Parkinson's disease. Further such models can be used for examination of behaviour during the

development of a neurodegenerative disease, for examination of physiological and molecular biological correlation of the disease, for studies of drug effects and for determination of effective drug doses and toxicity. These applications should be considered as examples and should 5 not limit the application of the models in any way.

The present invention provides model systems of neurodegenerative diseases, preferred Parkinson's disease, wherein the model system comprises a mutated isoform or a fragment of the mouse parkin2 gene 10 (further designated as *mPark2*), a DNA sequence derived from SEQ ID NO: 1 encoding a mouse parkin2 protein corresponding to the human parkin protein encoded by human chromosome gene region 6q25.2-27 ("PARK 2" gene locus). Preferred the model system contains a mutated *mPark2* sequence or a *mPark2* sequence containing any deletion, coding for a mutated or truncated, less 15 active or non-active parkin protein.

The sequence of human  $\alpha$ -synuclein (*parkin1*) gene, as well as human parkin (*parkin2*) gene is known. Human parkin2 gene (further designated as *hPark2*) contains 12 exons, coding for a protein which has in full length 465 amino 20 acids and a molecular weight of 51,652 Daltons.

The present application shows the full length cDNA of *mPark2* in SEQ ID NO:1, consisting of 12 exons, containing the full length open reading frame for the mouse parkin2 protein (SEQ ID NO:4) which coding region 25 consists of 1395 bp, coding for a protein of 464 amino acids with a calculated molecular weight of 51615 Dalton. Further two shorter cDNAs spanning a coding region of 789 bp (SEQ ID NO: 2 (isolated from mouse brain cDNA library by specific PCR)) and 753 bp (SEQ ID NO: 3 (isolated from mouse kidney cDNA library by specific PCR)) corresponding to amino 30 acid sequences of 262 amino acids (SEQ ID NO:5) and 250 amino acids (SEQ ID NO:6) respectively are provided.

During the work of isolation and sequencing of the sequences SEQ ID NO: 1 to 3 shown in this application Shimizu, N. et al. submitted a mouse parkin DNA sequence to the EMBL GenBank database, published in July 1999 with the accession number AB019558. The protein sequence of the mouse parkin  
5 protein encoded by the published sequence is identical to SEQ ID No: 4.

The present invention refers to polynucleic acid sequences derived from SEQ ID NO: 1, containing naturally occurring or artificially introduced mutations or deletions, which are known to cause Parkinson's disease in a  
10 human if they occur in the according human sequence.

The present invention encompasses further polynucleotide sequences containing naturally occurring mutations according to the wobble principle, which represents the degeneration of the genetical code, as  
15 well as according to the polymorphism of the genetical code, encoding any protein which has the same or a homologous amino acid sequence as any of the mutated or truncated mouse parkin2 proteins of the present invention.

"Homologous amino acid sequence" in content with the mouse parkin2 protein  
20 means in the present application an amino acid sequence, wherein at least 70 %, preferably 80 %, more preferably 90 % of the amino acids are identical to one of the proteins of the present invention and wherein the replaced amino acids preferably are replaced by homologous amino acids. As "homologous" amino acids are designated which have similar features  
25 concerning hydrophobicity, charge, steric features etc. Most preferred are amino acid sequences, containing the species-dependent differences of the mouse amino acid sequence compared to human parkin protein shown in the alignment Figure No. 1. The alignment of the corresponding polynucleotide sequences with the exon boundaries is shown in Figure No. 2.

In the whole application for nucleotides and amino acids the usual designations (one-letter or three-letter code) are used, known by any person skilled in the art.

5 The full length polynucleotide sequence of SEQ ID NO:1 or fragments thereof can be obtained by isolation of genomic DNA, containing exons and introns of the mPark2 gene, by RNA transcripts of the DNA or by the preparation of cDNA, containing only the exons of the mPark2 gene. Further the full length sequence as well as fragments thereof may be obtained by  
10 synthetical polymerisation of nucleotides.

A preferred polynucleotide sequence of the present application is a polynucleotide sequence derived from SEQ ID NO: 1, which is either mutated or in which parts of the sequence are deleted. Mutations, insertions or  
15 deletions may be located 5' upstream of the open reading frame (i.e. in the promotor-region), or they can concern one or more exons of the open reading frame. More preferred is a sequence, containing either a mutated full length sequence or fragments of SEQ ID NO:1, encoding a truncated parkin2 protein (i.e. by mutations leading to a STOP codon or by  
20 deletions) or no protein (i.e. if the mutation or deletion is located in the promoter-region in exon 1).

More preferred mutations or deletions concern either exon 1, wherein the promotor region is contained, or exon 3 and/or one or more of the other  
25 exons.

Most preferred the polynucleotide sequence of the present application is selected from SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID  
30 NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17; SEQ ID NO: 18, SEQ ID NO:19 or SEQ ID NO:20 (see also Table 1 and 2).

One of the polynucleotide sequences SEQ ID NO:1 to 3 may be treated *in vitro* or *in vivo* by random or site-directed mutagenesis, by random or site-directed digestion, by recombination or fusion or any other method known of persons skilled in the art to obtain sequences derived from SEQ 5 ID NO:1 containing mutations or deletions leading to a less active or to no parkin protein. Of course a person skilled in the art will understand that the present invention encompasses as well any construction in which parts of or the whole polynucleotide sequence encoding the parkin gene is deleted or replaced by another sequence (i.e. by a sequence encoding an 10 antibioticum-resistance).

To obtain at least a transgenic non-human animal as a model for neurodegenerative diseases, the natural occurring sequence of the parkin gene in this animal may be replaced on one or both alleles of the 15 chromosomes by a sequence of mPark2, containing mutations or deletions according to the present invention. These animals produce either less or less active or no parkin protein.

The transgenic animals of the present invention are created using targeted 20 gene replacement, a sequence by which a specific DNA sequence of interest (target DNA) is replaced by an altered DNA (replacement DNA). The genome of embryonic stem (ES) cells is modified using homologous recombination (Capecchi, Science 1989; 244:1288 and U.S. Pat. No. 5,487,992). The embryonic stem cells are injected in blastocysts as an early state of the 25 developing embryo. The blastocysts are then placed in a pseudopregnant female animal.

Briefly, a vector is constructed that carries the replacement DNA. Both ends of the replacement DNA are flanked by long DNA sequences homologous 30 to the sequences flanking the target DNA. When the vector is introduced into ES cells, the homologous sequences align and recombination may take place. This results in the target DNA being exchanged for the replacement

DNA. The vector is not replicated in the cells and will be lost. The frequency of homologous recombination is low; thus, a screening system is used. The replacement DNA will contain a positive marker sequence, usually a neomycin resistance gene. Thus, any cells that incorporate the

5 replacement DNA by homologous recombination will resist neomycin. By growing cells in medium containing the drug neomycin one can select only those cells containing the replacement DNA. The ES cells containing the replacement DNA are then inserted into recipient mouse blastocysts to create chimeric mice. Chimeras with germ cells derived from the altered ES

10 cells transmit the modified genome to their offspring, yielding mice heterozygous for the target DNA (contain one target DNA and one replacement DNA). The heterozygotes are then bred with each other either to create mice homozygous for the replacement DNA and deficient in the target DNA or to maintain transgenic heterozygotes if the homozygotic mice

15 are not viable.

The DNA will comprise at least a portion of the gene(s) at the particular locus with introduction of a lesion into at least one, usually both copies, of the native gene(s), so as to prevent expression of a functional

20 parkin protein. The lesion may be an insertion, deletion, replacement or combination thereof. When the lesion is introduced into only one copy of the gene being inactivated, the (heterozygote) cells having a single unmutated copy of the target gene are amplified and may be subjected to a second transformation, where the lesion may be the same or different from

25 the first lesion, usually different, and where a deletion, or replacement is involved, may be overlapping at least a portion of the lesion originally introduced. The resulting transformants are screened for the absence of the functional protein of interest and the DNA of the cell may be further screened to ensure the absence of a wild-type target gene.

30 Alternatively, homozygosity as to a phenotype may be achieved by breeding hosts heterozygous for the mutation.

For the construction of a transgenic animal model according to the present application any suitable animal may be employed, however mammals are preferred. More preferred are rodents and most preferred are rats and mice.

5

In the following the single steps of creating the animal models will be described in detail.

Starting from a polynucleotide sequence encoding a parkin gene, preferably 10 from a sequence encoding a mPark2 gene, more preferably from a sequence according to any of SEQ ID NO:1 to 3, most preferred from SEQ ID NO: 1 a desired mutation, insertion or deletion is introduced to the sequence. Methods to create mutations by random or site-directed mutagenesis or 15 desired insertions or deletions by random or site-directed digestion and/or replacement are commonly known to persons skilled in the art and broadly described in the literature. The method how a mutation, insertion or deletion is introduced in the sequence is not relevant, however falls under the scope of the present invention, as long as any of the later described nucleotides, amino acids or sequences are involved.

20

The constructs may be modified to include functional entities other than the mutated sequence which may find use in the preparation of the construct, amplification, transformation of the host cell, and integration of the construct into the host cell.

25

The homologous sequence for targeting the construct may have one or more deletions, insertions, substitutions or combinations thereof. For example, the mPark2 gene may include a deletion at one site and an insertion at another site which includes a gene which may be used for selection, where 30 the presence of the inserted gene will result in a defective inactive protein product. Preferably, substitutions are employed. For an inserted gene, of particular interest is a gene which provides a marker, e.g.,

antibiotic resistance such as neomycin resistance, including G418 resistance.

The deletion will be at least about 50 bp, or more usually at least about

5 100 bp, and generally not more than about 20 kbp, where the deletion will normally include at least a portion of the coding region including a portion of or one or more exons, a portion of one or more introns, and may or may not include a portion of the flanking non-coding regions, particularly the 5'-non-coding region (transcriptional regulatory region).

10 Thus, the homologous region may extend beyond the coding region into the 5'-non-coding region or alternatively into the 3'-non-coding region. Insertions will generally not exceed 10 kbp, usually not exceed 5 kbp, generally being at least 50 bp, more usually at least 200 bp.

15 The homologous sequence should include at least about 100 bp, preferably at least about 150 bp, more preferably at least about 300 bp of the target sequence and generally not exceeding 20 kbp, usually not exceeding 10 kbp, preferably less than about a total of 5 kbp, usually having at least about 50 bp on opposite sides of the insertion and/or the deletion in order to

20 provide for double crossover recombination.

Upstream and/or downstream from the target gene construct may be a gene which provides a tool to select out primary random integration of the construct in the genome. For this purpose, the herpes simplex virus

25 thymidine kinase gene may be employed, since the presence of the thymidine kinase gene may be detected by the use of nucleoside analogs, such as Gancyclovir or Acyclovir, for their cytotoxic effects on cells that contain a functional HSV-tk gene. The absence of sensitivity to these nucleoside analogs indicates that homologous recombination has occurred.

The presence of the marker gene inserted into the gene of interest establishes the integration of the target construct into the host genome.

However, DNA analysis might be required in order to establish whether homologous or non-homologous recombination occurred. This can be determined by employing probes for the insert and then sequencing the 5' and 3' regions flanking the insert for the presence of the gene of interest extending beyond the flanking regions of the construct or identifying the presence of a deletion, when such deletion is introduced.

The polymerase chain reaction (PCR) may be used, with advantage in detecting the presence of homologous recombination (Kim and Smithies,

10 (1988) Nucleic Acid Res. 16:8887-8903; and Joyner et al (1989) Nature 338:153-156). Primers may be used which are complementary to a sequence within the construct, usually complementary to the selection marker gene, and complementary to a sequence outside the construct and at the target locus. In this way, one can only obtain DNA duplexes having both of the  
15 primers present in the complementary chains in homologous recombination has occurred. By demonstrating the presence of the primer sequences or the expected size sequence, the occurrence of homologous recombination is supported. Any person skilled in the art knows how to determine the suitable PCR primers and conditions.

20 The construct may further include a replication system which is functional in the mammalian host cell. For the most part, these replication systems will involve viral replication systems, such as Simian Virus 40, Epstein-Barr virus, papilloma virus, adenovirus and the like.

25 Where a marker gene is involved, as an insert, and/or flanking gene, depending upon the nature of the gene, it may have the wild-type transcriptional regulatory regions, particularly the transcriptional initiation regulatory region or a different transcriptional initiation  
30 region. Whenever a gene is from a host where the transcriptional initiation region is not recognized by the transcriptional machinery of the mammalian host cell, a different transcriptional initiation region

will be required. This region may be constitutive or inducible, preferably inducible. A wide variety of transcriptional initiation regions have been isolated and used with different genes. Of particular interest as promoters are the promoters of metallothionein-I and II from a mammalian host, thymidine kinase, beta-actin, immunoglobulin promoter, human cytomegalovirus promoters, and SV40 promoters. In addition to the promoter, the wild-type enhancer may be present or an enhancer from a different gene may be joined to the promoter region.

10 The construct may further include a replication system for prokaryotes, particularly *E. coli*, for use in preparing the construct, cloning after each manipulation, allowing for analysis, such as restriction mapping or sequencing, followed by expansion of a clone and isolation of the plasmid for further manipulation. When necessary, a different marker may be

15 employed for detecting bacterial transformants.

Once the vector has been prepared, it may be further manipulated by deletion of the bacterial sequences as well as linearisation, where a short deletion may be provided in the homologous sequence, generally not exceeding about 500 bp, generally being from about 50 to 300 bp. The small deletion will generally be near one or other end of the targeted structural gene.

The construction of the desired polynucleotide sequence may be carried out

25 in a cloning vector and linearised prior to the transfection of ES cells. A broad range of cloning vectors as well as vectors for the homologous recombination are commercially available and may be selected according to the desired construction.

30 Cloning vectors are usually replicated in prokaryotic cells, which renders the selection and multiplication of the desired construct. It is not

critical which prokaryotic organism is used, but usually E.coli or a yeast strain is preferred.

E. coli is one prokaryotic host useful particularly for cloning the DNA sequences of the present invention. Other microbial hosts suitable for use include bacilli, such as *Bacillus subtilis*, and other enterobacteriaceae, such as *Salmonella*, *Serratia*, and various *Pseudomonas* species. In these prokaryotic hosts, one can also make expression vectors, which will typically contain expression control sequences compatible with the host cell (e.g., an origin of replication). In addition, any number of a variety of well-known promoters will be present, such as the lactose promoter system, a tryptophan (trp) promoter system, a beta-lactamase promoter system, or a promoter system from phage lambda. The promoters will typically control expression, optionally with an operator sequence, and have ribosome binding site sequences and the like, for initiating and completing transcription and translation.

Other microbes, such as yeast, may also be used for expression. *Saccharomyces* is a preferred host, with suitable vectors having expression control sequences, such as promoters, including 3-phosphoglycerate kinase or other glycolytic enzymes, and an origin of replication, termination sequences and the like as desired.

Homologous recombination may be used to insert a mutant sequence into a host genome at a specific site, for example, at a host parkin locus. In one type of homologous recombination, one or more host sequence(s) are replaced; for example, a host parkin allele (or portion thereof) is replaced with a mutant parkin allele (or portion thereof). In addition to such gene replacement methods, homologous recombination may be used to target a mutant parkin allele to a specific site other than a host parkin locus. Homologous recombination may be used to produce transgenic non-human animals and/or cells that incorporate mutant parkin alleles.

Further to the above described techniques a step of expressing the treated sequence may be inserted in the expiration. Therefore the construct is (sub)cloned into any expression vector, which may be brought into a

5 suitable eukaryotic cell. These expression vectors are typically replicable in the host organisms either as episomes or as an integral part of the host chromosomal DNA. Commonly, expression vectors will contain selection markers, e.g., tetracycline resistance or hygromycin resistance, to permit detection and/or selection of those cells transformed with the

10 desired DNA sequences. Polynucleotides encoding a variant parkin2 polypeptide may include sequences that facilitate transcription (expression sequences) and translation of the coding sequences, such that the encoded polypeptide product is produced. Construction of such polynucleotides is well known in the art and is described further in

15 Maniatis et al. Molecular Cloning: A Laboratory Manual, 2nd Ed. (1989), Cold Spring Harbor, N.Y. For example, but not for limitation, such polynucleotides can include a promoter, a transcription termination site (polyadenylation site in eukaryotic expression hosts), a ribosome binding site, and, optionally, an enhancer for use in eukaryotic expression hosts,

20 and, optionally, sequences necessary for replication of a vector.

Any suitable eukaryotic cell may be used, but insect cells or mammalian cells as primary cells or immortalized cell lines are preferred.

25 A number of suitable host cell lines capable of secreting intact human proteins have been developed in the art, and include the CHO cell lines, various COS cell lines, HeLa cells, myeloma cell lines, Jurkat cells, etc. Baculovirus expression systems are useful for high level expression of heterologous genes in eukaryotic cells. Knops et al. (1991) J. Biol. Chem.

30 266(11):7285. Expression vectors for these cells can include expression control sequences, such as an origin of replication, a promoter, an enhancer (Queen et al. (1986) Immunol. Rev. 89:49, and necessary

processing information sites, such as ribosome binding sites, RNA splice sites, polyadenylation sites, and transcriptional terminator sequences.

Preferred expression control sequences are promoters derived from immunoglobulin genes, SV40, Adenovirus, Bovine Papilloma Virus, and the

5 like. The vectors containing the DNA segments of interest can be transferred into the host cell by well-known methods, which vary depending on the type of cellular host. For example, calcium chloride transfection is commonly utilized for prokaryotic cells, whereas calcium phosphate treatment, microinjection of DNA into the nucleus or electroporation may 10 be used for other cellular hosts. (See, generally, Maniatis, et al.

Molecular Cloning: A Laboratory Manual, 2<sup>nd</sup>. Ed. Cold Spring Harbor Press, (1989). The DNA may be single or double stranded, linear or circular, relaxed or supercoiled DNA. For various techniques for transforming 15 mammalian cells, see Keown et al., Methods in Enzymology (1990) 185:527-

537.

For the creation of an animal model according to the present invention each polynucleotide sequence can be used, containing mutations, insertions

or deletions which are known to cause Parkinson's disease in a human, when 20 they occur in the corresponding human sequence. Preferred polynucleotide sequences for the creation of an animal model according to the present invention are those which mutations are shown in table 2. More preferred are polynucleotide sequences containing mutations or deletions shown in

table 1. The most preferred polynucleotide sequence for the construction 25 of a transgenic animal of the present invention is SEQ ID NO: 7

Further enclosed to the present invention is an animal model wherein the parkin sequence is replaced by an according sequence of another mammal (i.e. by the human sequence, containing one of the mutations, insertions or deletions described in the present application) or by a sequence 30 encoding a marker, i.e. an antibioticum.

Table 1: Mutations or deletions in mPark2 cDNA (SEQ ID NO:1)

| Position in<br>SEQ ID NO:1 | Replacement (DNA) | Replacement<br>(protein)       | SEQ ID NO<br>(DNA seq) | SEQ ID NO<br>(prot seq) |
|----------------------------|-------------------|--------------------------------|------------------------|-------------------------|
| NT 300-540                 | Exon3             | Frameshift,<br>Truncation      | 7                      | 21                      |
| NT 300-659                 | Exon3-4           | ORF, deletion of<br>121 aa     | 8                      | 22                      |
| NT 300-996                 | Exon3-7           | Frameshift,<br>Truncation      | 9                      | 23                      |
| NT 541-659                 | Exon 4            | Frameshift,<br>Truncation      | 10                     | 24                      |
| NT 659-744                 | Exon 5            | Frameshift,<br>Truncation      | 11                     | 25                      |
| NT 660-996                 | Exon 5-7          | Frameshift,<br>Truncation      | 12                     | 26                      |
| NT 996-1208                | Exon 8-9          | Frameshift,<br>Truncation      | 13                     | 27                      |
| NT: 229-230<br>(aa 34)     | deletion AG       | Gln→Stop at<br>aa 38, nonsense | 14                     | 28                      |
| NT: 282 (aa<br>52)         | deletion A        | Asn→Stop at<br>aa 54, nonsense | 15                     | 29                      |
| NT: 350-351<br>(aa 74)     | deletion AG       | Arg→Stop at<br>aa 78, nonsense | 16                     | 30                      |
| NT: 136-299                | Exon 2            | Frameshift,<br>Truncation      | 17                     | 31                      |

aa = amino acid

NT = nucleotide

Table 2: Replaced amino acids in mPark2 cDNA (SEQ ID NO:1)

| Position in<br>SEQ ID NO:1 | Replacement<br>(DNA) | Replacement<br>(protein) | SEQ ID NO<br>(DNA seq) | SEQ ID NO<br>(prot seq) |
|----------------------------|----------------------|--------------------------|------------------------|-------------------------|
| NT: 608                    | G→T,                 | Lys→Asn (aa 161)         | 18                     | 32                      |
| NT: 1369                   | C→A,                 | Thr→Asn (aa 415)         | 19                     | 33                      |
| NT: 1483                   | G→A,                 | Trp→Stop (aa 453)        | 20                     | 34                      |

aa = amino acid

5 NT = nucleotide

Once the construct has been prepared and manipulated, the DNA is isolated from the prokaryotic host according to any method known in the art. Before the DNA construct is introduced into the target cells for homologous recombination undesired sequences may be removed from the vector, e.g. the undesired bacterial sequences. As target cells an embryonic stem (ES) cell line may be used. As already indicated above for the expression system, any convenient technique for introducing the DNA into the target cells may be employed. After transformation of the target cells, many target cells are selected by means of positive and/or negative markers, as previously indicated, neomycin resistance and Acyclovir or Gancyclovir resistance. Those cells which show the desired phenotype may then be further analyzed by restriction analysis, electrophoresis, Southern analysis, polymerase chain reaction or the like. By identifying fragments which show the presence of the lesion(s) at the target gene site, one can identify cells in which homologous recombination has occurred to inactivate the target gene.

For embryonic stem cells, after mutation, the cells may be plated onto a feeder layer in an appropriate medium, e.g., fetal bovine serum enhanced DMEM. Cells containing the construct may be detected by employing a selective medium and after sufficient time for colonies to grow, colonies

may be picked and analyzed for the occurrence of homologous recombination. As described previously, the polymerase chain reaction may be used, with primers within and without the construct sequence but at the target locus. Those colonies which show homologous recombination may then be used for  
5 embryo manipulating by blastocyst injection. Blastocysts may be obtained from 4 to 6 week old superovulated females by flushing the uterus 3.5 days after ovulation. The embryonic stem cells may then be trypsinized and the modified cells added to a droplet containing the blastocysts. At least one, usually at least about 10, and up to about 15 of the modified  
10 embryonic stem cells may be injected into the blastocoel of the blastocyst. After injection, at least one and not more than about 15 of the blastocysts are returned to each uterine horn of pseudopregnant females. Alternatively, any of the common techniques, i.g. microinjection of the mutated gene, or a fragment thereof, into a one-cell embryo  
15 followed by incubation in a foster mother can be used.

The pups will usually be born 16-18 days after introduction of the blastocysts into foster mothers. Chimeric animals will be mated with wild type (wt) mice to create heterozygote transgenics.

20 With these methods it is possible to obtain transgenic non-human animals, whose one or both alleles of a gene encoding a parkin gene are mutated in a way, that a parkin protein with modified, preferred less activity or no active parkin protein is expressed.

25 "Mutated" means in this context replacements, insertions or deletions of nucleotides or polynucleotide sequences.

In consequence of the mutated parkin gene these animals produce a mutated  
30 or truncated parkin protein or no parkin protein. Preferred - if a parkin protein is expressed - the parkin protein expressed by the transgenic animal contains any of the mutations or deletions shown in table 1 and 2.

represented by any of the proteins with an amino acid sequence of SEQ ID NO:5, SEQ ID NO:6, SEQ, ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID

5 NO:34 or naturally occurring or artificially introduced mutants with a homologous protein sequence or fragments thereof, particularly preferred a parkin protein with a sequence according to SEQ ID NO:21 is expressed.

The expression of one of these proteins or no parkin protein in the

10 transgenic non-human animals causes these animals to display features of a neurodegenerative disease. These features can be manifested in developing physiological, biochemical or molecular biological modifications in e.g. cells, tissues, organs or neuronal structures.

15 In accordance with standard protocols, cultured eukaryotic cells, either primary cultures or immortalised cell lines, may be transfected, either transiently or stably, with a mutant or fragmented mPark2 allele so that the cultured eukaryotic cell expresses a mutant parkin2 polypeptide.

20 The present application further refers to cells, typically mammalian cells and preferably mammalian cells of the neural, glial, or astrocytic lineage, that have been transformed or transfected with any DNA sequence according to the present invention, as well as to any cells which have been derived from a transgenic non-human animal, whereby the cells express  
25 any of the mutated parkin2 proteins isoforms according to the present invention, preferred any of the isoforms shown in table 1 or 2 or fragments thereof, or they contain a parkin sequence which is mutated in a way that they don't express a parkin protein. The cells derived from the transgenic animals may be cultured as cell-lines or as primary cultures.

Once established, all such cell lines can be grown continuously in culture and may be used for a variety of in vitro experiments to study parkin expression and processing.

5 The present invention further refers to a method of producing transgenic non-human animals and transformed cells that contain any polynucleotide sequence encoding any mutant mouse parkin2 protein isoform according to the present invention, preferably such as shown in table 1 or 2 or naturally occurring or artificially introduced mutants or fragments  
10 thereof.

Preferred the above described polynucleotide sequences, the proteins and amino acid sequences as well as the transgenic animal models and cell lines may be used for any method for analysing the symptoms of  
15 neurodegenerative diseases.

Such neurodegenerative diseases encompass among others Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, Multisystem atrophy, Wilson's disease, Pick's disease, Prion  
20 disease, or second causes inducing Parkinson's syndromes like toxins (e.g. Mn, Fe, 6-hydroxydopamine, MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), CO), drugs, brain tumors, head trauma, stroke, vascular irregularities, or metabolic irregularities.

25 Enclosed to these methods are methods outside of a living body, which are methods of molecular biology like PCR, Southern and Northern blot analysis, construction of DNA or RNA probes, as well as Western blot analysis, preparation of epitopes from the protein or amino acid sequences mentioned in this application, production of monoclonal and polyclonal  
30 antibodies. These methods may be used for screening of samples, preferred of biological fluids for either the expression of parkin protein as a method for detecting the presence of the protein, or in a nucleic acid

sample or another sample removed from a subject, the presence of the gene for Parkinson's disease comprising identifying a genetic alteration in a gene sequence coding for parkin. Further enclosed are pathobiochemical, immunobiological and neurological as well as histochemical methods carried out after sacrificing the animal for considering the effects of neurodegenerative diseases, particularly Parkinson's disease to the living body. Further methods for locating the presence of genetic alterations associated with Parkinson's disease are provided. These methods may be used outside of a living body to predict the development of the disease prior to onset or for genetic screening.

However, particularly preferred is a method of testing the efficacy of a treatment for a neurodegenerative disease associated with a less active or non-active parkin protein, comprising subjecting any of the created transgenic animals as a model to a putative treatment and determining the efficacy of said treatment.

These testing methods preferably comprise administering an active substance, whose effect can be determined by any of the above described methods, to a transgenic animal according to the present invention.

By the use of the transgenic animals described in the present application it is possible the first time to test in a model system whether an active substance is useful for treating a condition associated with non-active parkin protein and determining a level of the active substance, which causes an effect in treating the disease.

Treatments may carried out as single dose applications, but it is preferred to use the transgenic animals in long-time experiments with multiple dose applications.

The transgenic animals of the present application may be particularly used as model systems for screening for drugs and evaluating drug effectiveness. Additionally, such model systems provide a tool for defining the underlying biochemistry of neurodegenerative diseases, which

5 thereby provides a basis for rational drug design. The models may be used further for studies of behaviour, physiological and molecular biological examinations, pharmacological and toxicological studies and several other applications.

10 Having detected the genetic mutation in the gene sequence coding for parkin protein in an individual not yet showing overt signs of Parkinson's disease, using any of the methods of the present invention, it may be possible to employ gene therapy, in the form of gene implants, to prevent the development of the disease.

15 Additional embodiments directed to modulation of the production of variant parkin proteins include methods that employ specific antisense polynucleotides complementary to all or part of a variant parkin sequence according to any of the sequences mentioned in this application, or for  
20 some embodiments a wild-type parkin sequence. Such complementary antisense polynucleotides may include nucleotide substitutions, additions, deletions, or transpositions, so long as specific hybridisation to the relevant target sequence is retained as a property of the polynucleotide. Thus, an antisense polynucleotide must preferentially bind to a variant  
25 parkin sequence as compared to a wild-type parkin. It is mostly preferred that the antisense polynucleotide reflects the exact nucleotide sequence of the variant allele (or wild-type allele where desired) and not a degenerate sequence.

30 Complementary antisense polynucleotides include soluble antisense RNA or DNA oligonucleotides which can hybridise specifically to a variant parkin mRNA species and prevent transcription of the mRNA species and/or

translation of the encoded polypeptide (Ching et al. (1989) Proc. Natl. Acad. Sci. U.S.A. 86:10006; Broder et al. (1990) Ann. Int. Med. 113:604; Loreau et al. (1990) FEBS Letters 274:53-56); Holcenberg et al. W091/11535; U.S. Pat. No. 7,530,165 ("New human CRIPTO gene"--publicly available through Derwent Publications Ltd., Rochdale House, 128 Theobalds Road, London, UK); W091/09865; W091/04753; W090/13641; and EP 386563, each of which is incorporated herein by reference). The antisense polynucleotides therefore inhibit production of the variant parkin polypeptides.

10

Antisense polynucleotides may be produced from a heterologous expression cassette in a transfectant cell or transgenic cell or animal, such as a transgenic neural, glial, or astrocytic cell, preferably where the expression cassette contains a sequence that promotes cell-type specific expression (Wirak et al. loc. cit.). Alternatively, the antisense polynucleotides may comprise soluble oligonucleotides that are administered to the external milieu, either in the culture medium *in vitro* or in the circulatory system or interstitial fluid *in vivo*. Soluble antisense polynucleotides present in the external milieu have been shown to gain access to the cytoplasm and inhibit translation of specific mRNA species. In some embodiments the antisense polynucleotides comprise methylphosphonate moieties. For general methods relating to antisense polynucleotides, see Antisense RNA and DNA, (1988), D. A. Melton, Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.).

25

Legends to the figures:

Figure 1 shows the alignment of the deduced amino acid sequences of the human and mouse Parkin2 protein (SEQ ID NO: 4).

30 Underlined are the conserved ubiquitin like (at the N-terminus) and Ring finger like (at the C-terminus) regions of both proteins.

Figure 2 shows the alignment of the nucleotide sequences of the human and mouse parkin 2 gene. Bold lines represent the exon boundaries identified for the human and mouse sequence.

5 Figure 3 represents a flow chart of the cloning procedure of the mouse parkin2 gene - exon3 knock-out construct.

Abbreviations:

a) Restriction endonucleases:

N = NotI, E= Eco RI, B= BamHI, H= HindIII, X= XbaI.

10 b) Modifications: ()= T4 DNA polymerase treatment in order to remove a restriction site in the resulting plasmid.

c)  pBluescript KSII (Stratagene) vector sequence  
 = λ-Fix vector sequence

d) HSV-tk = herpes simples promotor and thymidine kinase gene

15 e) kb = kilobases

The following examples are provided for illustration and are not intended to limit the invention to the specific example provided.

20 Example 1

Isolation of mouse Parkin2 cDNA clones:

25 Arrayed mouse brain and mouse kidney cDNA libraries (Biofrontera Pharmaceuticals/ Bio Systems) were screened by PCR under standard conditions using the primers Ex2s:*tcaggttcaactccagctatggc* and Ex2as: *tgcctgcgaaaatcacacgcagc*. The cycle conditions were the following: 3 min. 95°C, (30sec. 95°C, 30sec. 56°C, 1min. 72°C) x 35 cycles.

Single colonies containing the mPark2 genes were verified by colony hybridisation according to the protocol described by Maniatis *et al.* 1989 (see above).

5 Construction of the Del Exon3 parkin gene (according to SEQ ID NO: 7)

All the further described cloning steps are shown in Figure 3. A genomic lambda ZIP clone (genomic mouse  $\lambda$ -Fix library, Stratagene) containing the exon 3 of the parkin gene was isolated by PCR using exon3 specific primer 10 of the mPark2 gene. A 3.1 kb BamHI/HindIII fragment of the lambda ZIP clone containing genomic DNA 3' end to the exon3 of mPark2 was cloned into the cloning vector pBluescript KS (Stratagene) to obtain the plasmid pmPark2-BH. Secondly, a 5 kb HindIII/EcoRI genomic DNA fragment was inserted into the HindIII site of the pmPark2-BH-clone. The EcoRI and 15 HindIII sites were destroyed by T4 DNA polymerase treatment. As result the plasmid pmPark2-BE- with a 8.1 kb long genomic region to the 3'-end of the exon 3 could be obtained.

A 2.0 kb XbaI/XhoI (the XbaI restriction site is located within the 20 multiple cloning sequence (mcs) of Lambda Fix) genomic DNA fragment containing the genomic region 5' to the exon3 was cloned into the EcoRI site of the pNeoloxp-vector (Giese *et al.* Science, 1998, 279:870-3 ) after generation of blunt ends by T4 DNA polymerase treatment. The BamHI-site (5'-to the EcoRI-site) of this vector was used subsequently for the 25 insertion of the 2.5 kb HSV-tk-marker gene. Again T4 DNA polymerase was used to generate blunt ends before ligation in order to eliminate the used cloning site. The resulting vector was digested with the restriction enzymes NotI and XhoI to obtain a 6.5 kb fragment containing the HSV-tk, the 2kb XhoI/XbaI genomic region to 5'-end of exon3, and the neo-marker. 30 The vector pmPark2-BE was digested with XhoI to linearise the plasmid. Both the isolated 6.5 kb fragment as well as the linear vector were

treated with T4 DNA polymerase prior to ligation to eliminate the used restriction sites.

This plasmid pmPark2del-ex3 was linearised with the restriction enzyme

5 NotI prior to transfection into ES cells.

#### Example 2

##### Transfection of ES cells:

10

##### Isolation and Freezing of the ES cells:

14 days old embryos were isolated, head and organs were removed from embryos, the remaining tissue was minced, and washed with 1x PBS. 1x trypsin (0,5g/l) / EDTA (0,2g/l) was used for dissolve the tissue by

15 incubating them at 37°C for 5 min. The reaction was stopped by adding 1 vol. EF medium (Embryonic Feeder medium: 1x DMEM, 10% FCS Serum, 2mM Glutamine, all obtained from LIFE Technologies), and cells were dissolved by pipetting several time up and down. The supernatant was centrifuged with 1000 rpm for 5 min. The fibroblasts from one embryo were seeded into 20 a 175 cm<sup>2</sup> flask with 30 ml medium. The medium was changed after 24 h. When the fibroblasts form a confluent monolayer they were splitted 1:3, and thereafter they were frozen when the cells are confluent again. Cells from 175 cm<sup>2</sup> flask were frozen into one tube. Therefore first empty tubes are place on ice, freezing medium is added (EF medium + 20% DMSO 25 (Dimethylsulfoxid)), cells with 0.5 ml EF medium are added, mixed, putted in a styrofoam box, which is cooled down in a -80°C freezer, and the next day the tubes are transferred into liquid N<sub>2</sub>(l) tank.

##### Sub-culturing, inactivation and feeder layer:

30 The fibroblasts can be cultured on gelatine-coated plastic ware. The cells were splitted carefully 1:3 after 3 days. When feeder layer are needed for ES cell culturing, the fibroblasts should be division-inactivated by

mitomycin C. 2 mg mitomycin C are dissolved in 10 ml PBS, which can be stored at -20°C. This stock solution is diluted 1:20 with EF medium for inactivation; the nearly confluent fibroblasts in a 175 cm<sup>2</sup> flask are incubated in 20-30 ml of medium with mitomycin C for 2 h at 37°C.

- 5 Mitomycin C is then removed by 2x washing with PBS, and the inactivated fibroblasts are recovered in EF medium for 24 h before they are frozen or used for ES cell culturing after a few days. The cells are stored 37°C until they are used (maximally 10 days;) or they are frozen. For feeder layer, plate cells onto the same area; here the plastic ware has to be  
10 coated by gelatine.

#### Sub-culturing the ES-cells:

The ES cells were kept for 2-4 passages in culture. The medium is ES medium (1x DMEM, 15% FCS Serum, 2mM Glutamine, 1x nonessential amino acids, 7µl B Mercaptoethanol, with supplement containing LIF (Leukemia Inhibitory Factor, 2.5x10<sup>5</sup> to 10<sup>6</sup> U/l), all obtained from LIFE Technologies), and the cells are splitted 1:6 every second day. Cells were refeeded 2 h before passaging.

#### 20 Stable Transfection of ES Cells

After digestion of the gene targeting construct the DNA is extracted with phenol/CHCl<sub>3</sub> (24/23) and precipitated with EtOH (wash 2x with 75% EtOH); the rest of EtOH is removed carefully and air dried for approx. 15 min under steril conditions (laminar flow). The DNA is suspended in H<sub>2</sub>O (final conc.: 3 mg/ml). 5x10<sup>7</sup> cells of a monolayer are treated with 1x trypsin to detach them from the ground of the flask, suspended in 0.8 ml medium and electroporated with DNA (30 µg linear DNA, 800 V, 3 µF, BioRad Gene Pulser). After 20 min at 4°C, cells are diluted with 9.5 ml medium and are plated onto dishes (9 cm diameter). 24 h after electroporation G418 (150-30 175 mg /ml) is added to start selection. The medium is changed every day; after 7-9 days of selection colonies can be picked.

Picking colonies and culturing of picked colonies:

24 colonies were picked with Eppendorf tips under an inverted microscope.

The colonies were transferred into the wells of a 96-well plate (round bottom), 30 µl 1xtrypsin/EDTA are added, and the plates are incubated 10

5 min at 37°C. Thereafter 100 µl ES-medium are added and the cells are suspended by pipetting up and down 12x with a multichannel pipette. The trypsinized cells are solitarily plated into a 24-well plate. The medium is exchanged every 24 h. 3-4 days after picking the cells are detached from the ground of the plates. Therefore the medium is removed, 60 µl

10 1xtrypsin/EDTA are added and the plates are incubated for 7 min at 37°C.

The treatment is stopped by adding 200 µl medium and the cells are resuspended. 200 µl of the cell suspension is added to 200 ml medium with 20 % DMSO and the cells are frozen as described above.

15 Example 3

DNA isolation and southern blot analysis for control and identification of picked colonies:

To characterize the clones, picked in example 2, DNA is isolated from the

20 cells and examined. Therefore 500 µl medium are added into any well of a picked colony which should still contain 60 µl cell suspension (see

example 2). The cells are cultured continuously 3-4 days until confluent for DNA isolation. 500 µl lysis buffer (12 ml 1 M Tris-HCl (pH 8.3); 1.2 ml 0.5 M EDTA; 2.4 ml 10 % SDS; 4.8 ml 5 M NaCl; 1.2 ml 10 mg/ml

25 proteinase K; 98.4 ml H<sub>2</sub>O) is added, and it is incubated over night at 55°C. DNA is precipitated by adding 1 vol. 2-propanol and at least 15 min shaking at RT, and transferred with an Eppendorf tip into a 1.5 ml tube with 1 ml 70% EtOH. The tube is centrifuged for 10 min at RT to spin down the DNA. EtOH is removed and pellets are air dried for least one hour. DNA 30 is dissolved afterward in 100 µl TE for over night at 55°C.

Southern blot analysis:

1/3 of the isolated DNA was used for one digestion. The digestion was carried out for over night at 37°C. Loading buffer was added, and DNAs are separated in an agarose gel for least 6 hours. The gels were incubated in 0.2 N HCl for 15 min at room temperature; after 15 min HCl solution was

5 replaced by 0.4 N NaOH and the gel was incubated therein for 15 min at RT. The DNA was transferred onto nylon membranes (Amersham) over night using 0.4 N NaOH as transfer buffer using a vacuum blot machine (Stratagene). The membranes were neutralized in 2x SSC for 1 min, and air dried for least one hour. After UV-Crosslinking the DNA onto the membrane  
10 hybridisation with DNA probes (probes are shown in figure 3) was carried out under standard conditions (QuickHyb from Clontech, 65°C, wash twice with 2x SSC, 0.1 % SDS at 65°C).

Production of transgenic animals with mutant parkin allele:

15 10-15 recombinant ES cells are injected into blastocysts. The blastocysts are implanted in pseudopregnant mice. The chimeric spring offs are crossed with wild type mice to obtain heterozygotic recombinant F1 mice. These mice are analysed by southern blot analysis as described above. Transgenic  
20 mice are crossed with each other to obtain mice with both alleles modified (homozygote animals).

Descendants of the transgenic animals may be used for breeding with mice strains representing the same or any other genotype, preferred mice  
25 strains showing neurological abnormalities, more preferred with strains showing neurodegenerative abnormalities. These other mouse strains may be selected from wild type mice, mice containing knock-ins or knock-outs, mice containing mutants of genes or mice which overexpress any gene product. The most preferred partners for breeding are mice which represent  
30 a model for Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, Multisystem atrophy, Wilson's disease, Pick's disease or Prion disease.

Use of Transgenic Mice:

The animal can be used to test potential therapeutic agents. The test  
5 group of mice is treated with the test compound administered in an appropriate fashion for a set period. At the conclusion of the test period, the animals are assessed behaviourally, biochemically, and histologically for any possible effects of the test compound. The exact protocol depends on the anticipated mechanism of action of the test  
10 compound. Compounds that may have utility in treating Parkinson's disease can be identified using this approach.

Such analysis can be carried out in the animal ,in primary tissue cultures of the expressing cells or in immortalised cells derived from those  
15 animals.

Mice expressing the truncated parkin2 protein gene or variants of the described one can be used for testing the development of Parkinson's disease during ageing of the animals. Beside the enhanced progression of  
20 cell death in substantia nigra area, increased sensitivity to selective neurotoxins like MPTP or 6-hydroxydopamine and enhanced response to dopaminergic precursors like L-dopa may be examined.

## Claims

1. A polynucleotide sequence encoding a mouse parkin2 protein, containing naturally occurring or artificially introduced mutations or deletions, which cause Parkinson's disease in a human if they occur in the according human sequence.
2. The sequence of claim 1, wherein the sequence is genomic DNA, coding for a full-length parkin gene or fragments thereof, cDNA of a full length parkin gene or fragments thereof, or RNA of a full length parkin gene or fragments thereof.
3. The sequence of claim 1 or 2, wherein the sequence is selected from the group, consisting of SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:7 SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20 or naturally occurring or artificially introduced mutants or fragments thereof.
- 20 4. A vector, containing any sequence according to any of claims 1 to 3.
5. A prokaryotic or eukaryotic cell, containing a vector according to claim 4.
- 25 6. The cell of claim 5, characterised in that the cell is selected from bacterial or yeast cells, insect cells or mammalian cells as primary cells or immortalised cell lines.
- 30 7. A parkin mouse protein with an amino acid sequence of SEQ ID NO:5, SEQ ID NO:6 SEQ, ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34 or

naturally occurring or artificially introduced mutants with a homologous protein sequence or fragments thereof.

8. A transgenic non-human animal, whose one or both alleles of a gene encoding a parkin gene are mutated or truncated in a way, that a protein with modified, preferred less activity or no active protein is expressed.
9. The transgenic animal of claim 8, wherein the parkin gene has any mutation or deletion which are known to cause Parkinson's disease in a human if they occur in the according human sequence.
10. The transgenic non-human animal of claim 8 or 9, carrying a mutation or deletion in one or both alleles of a gene encoding a parkin protein, such that expression of said parkin gene produces a mutated or truncated protein or no protein, which causes said animal to display any physiological, biochemical or molecular biological features of a neurodegenerative disease.
11. The transgenic non-human animal of claim 10, carrying a deletion in one or both alleles of any of the exons of the gene encoding the parkin protein.
12. The transgenic non-human animal of any of claims 8 to 11, carrying a DNA sequence according to any of the sequences SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:7 SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19 or SEQ ID NO:20.
13. A mammalian cell-line transformed or transfected with any sequence according to any of claims 1 to 3 or a vector according to claim 4 or

cell lines or primary cultures derived from the transgenic animal of any of claims 8 to 12.

14. A method of producing a transgenic animal according to any of claims  
5 8 to 12 or a cell line according to claim 13.

15. Use of the transgenic non-human animal according to any of claims 8 to 12 or a cell line according to claim 13 as a model for neurodegenerative diseases.

10 16. A method for analyzing the symptoms of neurodegenerative diseases, either outside of a living body using any of the polynucleotide sequences of any of claims 1 to 4, any of the protein sequences of claim 7, or using any model according to claim 15.

15 17. A method for testing the efficacy of a treatment for a neurodegenerative disease associated with a less active or non-active parkin protein, comprising subjecting any model of claim 15 to a putative treatment and determining the efficacy of said treatment.

20 18. The method according to claim 16 or 17, wherein said neurodegenerative disease is selected from the group consisting of Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, Multisystem atrophy, Wilson's disease, 25 Pick's disease, Prion disease, or second causes inducing Parkinson's syndromes like toxins, drugs, brain tumors, head trauma, stroke, vascular irregularities, or metabolic irregularities.

25 19. The method of any of claims 17 to 19, wherein said treatment 30 comprises administering an active substance to the model.

20. Use of any model according to claim 15 for testing whether an active substance is useful for treating a condition associated with non-active parkin protein comprising administering said active substance to the transgenic animal of any of claims 8 to 12 or a cell-line of claim 13, and determining a level of the active substance, which causes an effect in treating the disease.

21. Use of the animal according to any of claims 8 to 12 as a model for examination of behaviour during the development of a neurodegenerative disease, or any model according to claim 15 for examination of pathobiochemical, immunobiological, neurological as well as histochemical effects of neurodegenerative diseases, physiological and molecular biological correlation of the disease, for studies of drug effects and for determination of effective drug doses and toxicity.

15 22. Descendant of the transgenic animal according to any of claims 8 to 12, obtained by breeding with the same or any other genotype.

|                  |  |   |   |   |                                      |                    |
|------------------|--|---|---|---|--------------------------------------|--------------------|
| hPARK2<br>mPARK2 | 1 MIVFVREN <sub>S</sub><br>1 . . . . .       | 10 HGFPVEVD <sub>S</sub><br>Y . . . . . | 20 TSIFQLIKEV <sub>V</sub><br>L . . . . . | 30 AKRQGVPA <sub>D</sub><br>Q . . . . .     | 40 LRVIFAGKEL<br>. . . . .           | 50 50              |
| hPARK2<br>mPARK2 | 51 RNDWTVQNCD<br>51 P.HL.                    | 60 LDQOSIVHIV<br>E . . . . .            | 70 QRPWRKGQEM<br>T . . . . .              | 80 NATGGDDPRN<br>S . . . . .                | 90 AAGGCEREPQ<br>TSE . QS            | 100 TSE . SIW . SR |
| hPARK2<br>mPARK2 | 101 SLTRVDLSSS<br>101 . . . . .              | 110 VLPGDSVGLA<br>T . V . . . .         | 120 VILHTDSRKD<br>D . . . . .             | 130 SPPAGSPAGR<br>EA . RG .                 | 140 SIYNNSFYVYC<br>V-K . . . . .     | 150 FI . . . . .   |
| hPARK2<br>mPARK2 | 151 KGPCORVQPG<br>151 . . . . .              | 160 KLRVQCSICR<br>HK . . . . .          | 170 QATLTLTQGP<br>G . K . . . .           | 180 SCWDDVLIPN<br>A . . . . .               | 190 RMSGECQSPH<br>D . . . . .        | 200 200            |
| hPARK2<br>mPARK2 | 201 CPGTSAAE <sub>FFF</sub><br>201 . . . . . | 210 KCGAHPTSDK<br>R . . . . .           | 220 ETPVALHLIA<br>D . S . . . .           | 230 TNSRNITCIT<br>S . N . . . .             | 240 CTDVRSPVLV<br>S . R . S . P . A  | 250 250            |
| hPARK2<br>mPARK2 | 251 FQCNISRHVIC<br>251 . . . . .             | 260 LDCAFHLYCVT<br>H . . . . .          | 270 RLNDRQFVHD<br>T . . . . .             | 280 PQLGYSI <sub>L</sub> PCV<br>A . . . . . | 290 AGCPNSLIKE<br>A . . . . .        | 300 300            |
| hPARK2<br>mPARK2 | 301 LHHFRILGEE<br>301 . . . . .              | 310 QYNRYQQYGA<br>T . . . . .           | 320 EECVLOMGGV<br>T . . . . .             | 330 LCPRPGCGAG<br>T . . . . .               | 340 LLPEPDQRKV<br>T . . . . .        | 350 350            |
| hPARK2<br>mPARK2 | 351 TCEGGNGLLGC<br>351 . . . . .             | 360 GFAFCRECKE<br>V . . . . .           | 370 YHEGECCSAV<br>D . . . . .             | 380 FEASGTTQA<br>DDSL . . . . .             | 390 YRVVDERAAEQ<br>L . P . A . S . . | 400 400            |
| hPARK2<br>mPARK2 | 401 ARWEAASKET<br>401 . . . . .              | 410 IKKTTTKPCPR<br>E . . . . .          | 420 CHVPVEKNGG<br>N . . . . .             | 430 CMHMKCPQPQ<br>I . . . . .               | 440 CRLEWCWNCG<br>K . . . . .        | 450 450            |
| hPARK2<br>mPARK2 | 451 CEWNDRVCMGD<br>451 . . . . .             | 460 HWFDV*<br>A . . . . .               | 470 . . . . .                             | 480 . . . . .                               | 490 . . . . .                        | 500 500            |

2a/3

|        |     | 10          | 20          | 30           | 40          | 50  |
|--------|-----|-------------|-------------|--------------|-------------|-----|
| hPARK2 | 1   | TCCGG---    | GGA---TT-   | -----AC      | CCAGGAGAC-  |     |
| mpark2 | 1   | CT.A.CGAGG  | GGAAAGGGG   | ATGACTAA     | .TGAC..AA   | 50  |
| hPARK2 | 51  | CGCTGGGG    | AGGGGGG-C   | GCGGCCATGG   | GCCTGTTCCT  | 100 |
| mpark2 | 51  | .....T.     | G.....AG.   | ...C..G.A.   | .T.C..TC    | 100 |
| hPARK2 | 101 | GGCCGCAGC   | CGCCACCTAC  | CCAGTGACCA   | TGATAGTGT   | 150 |
| mpark2 | 101 | A.....A.    | A.....CG.   | G.....G.     | G.....G.    | 150 |
| hPARK2 | 151 | AACTCCAGCC  | ATGGTTCCC   | AGTGGGGTC    | CGAGCATCTT  | 200 |
| mpark2 | 151 | .....T      | .....C.     | .....C.      | .....C.     | 200 |
| hPARK2 | 201 | CGAGCTCAAG  | GAGGTGGTTG  | CTAACGGACA   | GGGGTTCGG   | 250 |
| mpark2 | 201 | .....A.     | .....A.     | .....A.      | .....A.     | 250 |
| hPARK2 | 251 | TGGCTGTGAT  | TTTCGCCAGG  | AAGGAGCTGA   | GACTGTGAG   | 300 |
| mpark2 | 251 | .....T.     | .....C.     | .....TC      | .....CT     | 300 |
| hPARK2 | 301 | ATTGTGACC   | TGGATCAGCA  | GAGCATTGTT   | CACATTGTC   | 350 |
| mpark2 | 301 | .....C.     | .....A.     | .....A.      | .....A.     | 350 |
| hPARK2 | 351 | GAGAAAAGT   | CAAGAAATGA  | ATGCAAATGG   | AGGCGAGAC   | 400 |
| mpark2 | 351 | .....G.G.A. | .....T.     | .....T.      | .....G.     | 400 |
| hPARK2 | 401 | CGGGGGAGG   | CTGTGAGGG   | GAGCCCCAGA   | GCTTGACTCG  | 450 |
| mpark2 | 401 | CT.A.AG     | .....C.CATA | .....T..AG.  | .....A.     | 450 |
| hPARK2 | 451 | AGCAGCTCAG  | TCCTCCAGG   | AGACTCTGTG   | GGGCTGGCTG  | 500 |
| mpark2 | 451 | .....ATA    | .....G.     | .....G.T     | .....G.     | 500 |
| hPARK2 | 501 | CACTGACAGC  | AGGAAGGACT  | CACCAACCAGC  | TGGAAGTCCA  | 550 |
| mpark2 | 501 | .....A.     | .....T.     | .....A..G.   | .....G.     | 550 |
| hPARK2 | 551 | CAATCTAAC   | CAGCTTTAT   | GTGTATTGCA   | GGAGCCCCCTG | 600 |
| mpark2 | 551 | .....C.C.   | .....TC     | .....A.C..C. | .....C..C.  | 600 |
| hPARK2 | 601 | CAGCCGGAA   | AACTCAGGGT  | ACAGTGGAGC   | ACCTGGAGGC  | 650 |
| mpark2 | 601 | .....T.     | .....G.     | .....C.A.    | .....AA.    | 650 |
| hPARK2 | 651 | CACCTTGACC  | CAGGGTCCAT  | CTTGCTGGGA   | TGATGTFTIA  | 700 |
| mpark2 | 651 | .....G.     | .....C.     | .....G.      | .....C.     | 700 |
| hPARK2 | 701 | GGATGAGTGG  | TGAATGCCAA  | TCCCCACACT   | GCCCTGGGAC  | 750 |
| mpark2 | 701 | .....G.     | .....G.     | .....T..G.   | .....A.     | 750 |
| hPARK2 | 751 | TTTTCTTTA   | AATGTGGAGC  | ACACCCACC    | TCTGACAAAGG | 800 |
| mpark2 | 751 | .....A.     | .....A.     | .....A.      | .....A.     | 800 |

Fig 2

2b/3

|                  |   |  |                                |                                |                              |                     |
|------------------|---|--|--------------------------------|--------------------------------|------------------------------|---------------------|
| hPARK2<br>mPark2 | 801 AGCTTTGCAC<br>801 . . . . A           | 810 CTGATCGCAA<br>. . . . A.C.           | 820 CAAATAGTCG<br>. . . . C.G. | 830 GAACATCACT<br>. . . . C.G. | 840 TGCATTACGT<br>. . . . AG | 850 850             |
| hPARK2<br>mPark2 | 851 GCACAGACGT<br>851 . . . . T           | 860 CAGGCCCC<br>. . . . T                | 870 880 890                    | 880 890                        | 900 900                      | 900 900 Exon6/7     |
| hPARK2<br>mPark2 | 901 GTGATTTGCT<br>901 . . . . C.T.        | 910 TAGACTGTT<br>. . . . G.T.            | 920 930 940                    | 930 940                        | 950 950                      | 950 950             |
| hPARK2<br>mPark2 | 951 TCGGCAGTT<br>951 . . . . A.G.         | 960 GTTCACGGACC<br>. . . . C.T.G.        | 970 980 990                    | 980 990                        | 1000 1000                    | 1000 1000 Exon7/8   |
| hPARK2<br>mPark2 | 1001 CTGGCTGTCC<br>1001 . . . . C         | 1010 CAACTCCTTG<br>. . . . C             | 1020 1030 1040                 | 1030 1040                      | 1050 1050                    | 1050 1050           |
| hPARK2<br>mPark2 | 1051 GGAGAAAGGC<br>1051 . . . . A         | 1060 ATTAACCCG<br>. . . . CTA            | 1070 1080 1090                 | 1070 1080                      | 1100 1100                    | 1100 1100 Exon8/9   |
| hPARK2<br>mPark2 | 1101 CCTGGCAGATG<br>1101 G.. . . A.. . .  | 1110 GGGGGCGTGT<br>. . . . A.. . . T     | 1120 1130 1140                 | 1120 1130 1140                 | 1150 1150                    | 1150 1150           |
| hPARK2<br>mPark2 | 1151 TGCTGCCGGA<br>1151 . . . . A.. . .   | 1160 GCCTGACCAG<br>. . . . A.. . . T     | 1170 1180 1190                 | 1170 1180 1190                 | 1200 1200                    | 1200 1200           |
| hPARK2<br>mPark2 | 1201 CTGGGGCTGTG<br>1201 . . . . C.. . .  | 1210 GGTTTGCGCTT<br>. . . . C.. . . C    | 1220 1230 1240                 | 1220 1230 1240                 | 1250 1250                    | 1250 1250 Exon9/10  |
| hPARK2<br>mPark2 | 1251 AGGGGAGTGGC<br>1251 . . . . T        | 1260 AGTGGCGTAT<br>. . . . GACT.AC.GC    | 1270 1280 1290                 | 1270 1280 1290                 | 1300 1300                    | 1300 1300 Exon10/11 |
| hPARK2<br>mPark2 | 1301 ACAGAGTCGA<br>1301 . . . . G.. . .   | 1310 TGAAGAGGCC<br>. . . . G.. . . CA    | 1320 1330 1340                 | 1320 1330 1340                 | 1350 1350                    | 1350 1350           |
| hPARK2<br>mPark2 | 1351 AAAGAAACCA<br>1351 . . . . G.. . .   | 1360 TCAAGAAAAAC<br>. . . . G.. . . G    | 1370 1380 1390                 | 1370 1380 1390                 | 1400 1400                    | 1400 1400           |
| hPARK2<br>mPark2 | 1401 AGTGGAAAAA<br>1401 . . . . A.. . .   | 1410 AATGGAGGCT<br>. . . . C.. . . A     | 1420 1430 1440                 | 1420 1430 1440                 | 1450 1450                    | 1450 1450 Exon11/12 |
| hPARK2<br>mPark2 | 1451 GCAGGGCTCGA<br>1451 . . . . A.. . .  | 1460 GTGGTGGCTGG<br>. . . . T            | 1470 1480 1490                 | 1470 1480 1490                 | 1500 1500                    | 1500 1500           |
| hPARK2<br>mPark2 | 1501 ATGGGGGAC<br>1501 . . . . A.. . .    | 1510 ACTGGTTCGA<br>. . . . T             | 1520 1530 1540                 | 1520 1530 1540                 | 1550 1550                    | 1550 1550           |
| hPARK2<br>mPark2 | 1551 GC-CACATCC<br>1551 A.G.. . . A.. . . | 1560 TGGGGGAGCA<br>. . . . CAA.. . . GAA | 1570 1580 1590                 | 1570 1580 1590                 | 1600 1600                    | 1600 1600           |

Fig 2

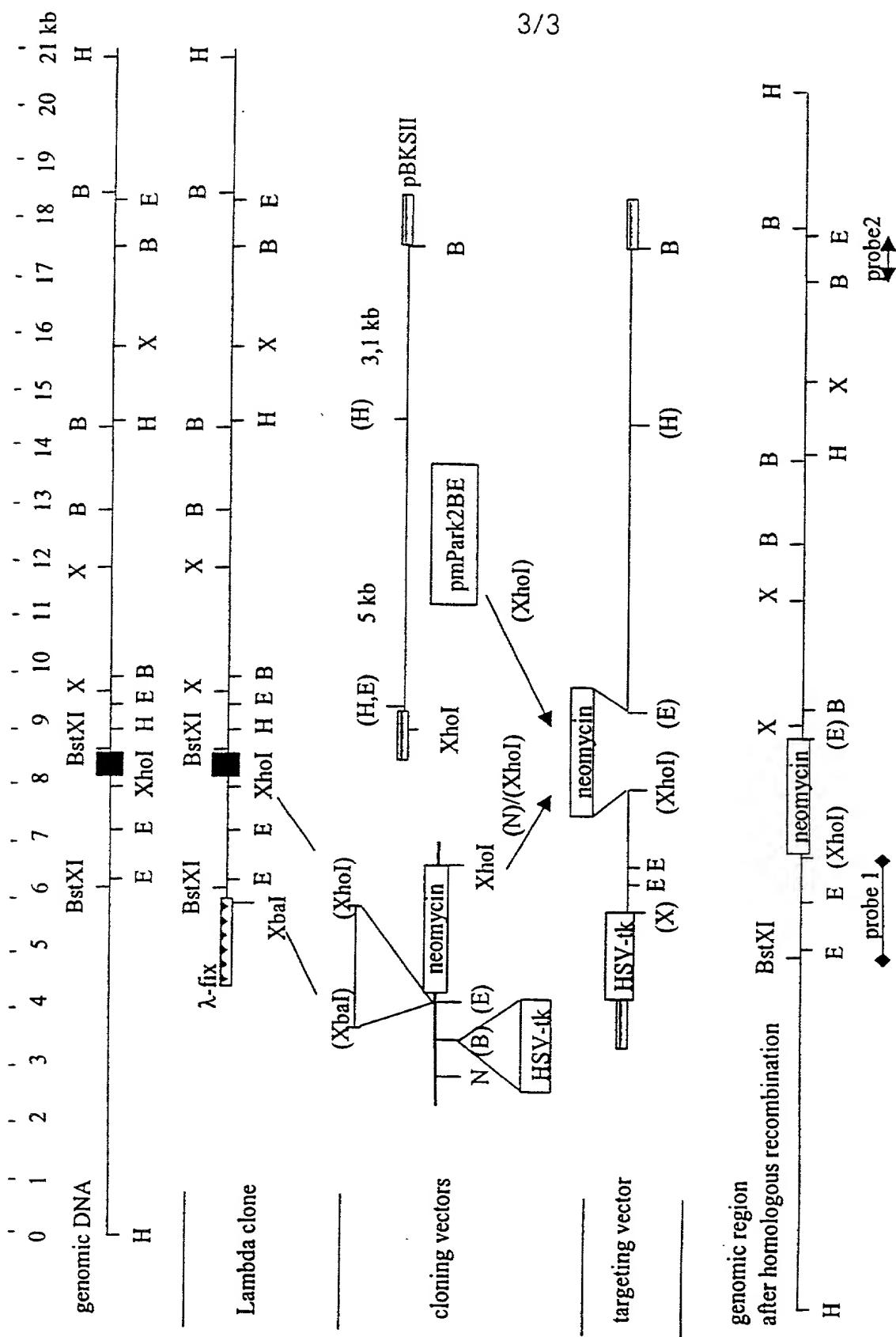


Fig 3

**DECLARATION & POWER OF ATTORNEY - USA PATENT APPLICATION**

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name;

I believe I am the original, first and sole inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled: **TRANSGENIC ANIMAL MODEL FOR NEURODEGENERATIVE DISEASES**, the specification of which:

- (a)  is attached hereto; or
- (b)  was filed on \_\_\_\_\_ as Application No. \_\_\_\_\_;  
or
- (c)  was described and claimed in PCT International Application No. **PCT/EP00/08071** filed on **August 18, 2000** and as amended under PCT Article 19 on \_\_\_\_\_ (if any) and/or under PCT Article 34 on \_\_\_\_\_ (if any).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above;

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, § 1.56;

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent, design or inventor's certificate or any PCT international application(s) listed below and have also identified below any foreign application(s) for patent, design or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed for the same subject matter having a filing date before that of the application(s) of which priority is claimed:

**PRIOR FOREIGN APPLICATION(S)**

| COUNTRY (OR INDICATE IF PCT) | APPLICATION NUMBER | DATE OF FILING<br>(day, month, year) | PRIORITY CLAIMED<br>UNDER 37 U.S.C. § 119                                |
|------------------------------|--------------------|--------------------------------------|--|
| Europe                       | 991167669          | 30/08/99                             | <input checked="" type="checkbox"/> YES      NO <input type="checkbox"/> |
|                              |                    |                                      | <input type="checkbox"/> YES      NO <input type="checkbox"/>            |
|                              |                    |                                      | <input type="checkbox"/> YES      NO <input type="checkbox"/>            |
|                              |                    |                                      | <input type="checkbox"/> YES      NO <input type="checkbox"/>            |

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below, and insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Prior U.S.A. Application(s)

| Application No. | Filing Date | Status |
|-----------------|-------------|--------|
| N/A             | N/A         | N/A    |

**POWER OF ATTORNEY:** I hereby appoint the registrants of Knobbe, Martens, Olson & Bear, LLP, 620 Newport Center Drive, Sixteenth Floor, Newport Beach, California 92660, Telephone (949) 760-0404, **Customer No. 20,995.**

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor: Hermann Lübbert

Inventor's signature O. L-LL Day 3 Month April Year 01

Residence (city and country): Leverkusen, Germany

Citizenship: German

Post Office Address: LÜBBERT, Hermann, Höhenstrasse 59, D-51381 Leverkusen, Germany

**Additional Inventors Listed on Attached Pages**

*DEX*

Send Correspondence To:

KNOBBE, MARTENS, OLSON & BEAR, LLP  
**Customer No. 20,995**

## SEQUENZPROTOKOLL

<110> Firma Biofrontera GmbH

<120> Transgenic animal model for neurodegenerative diseases

<130> 5807EPAlleSequenzen

<140>

<141>

<160> 34

<170> PatentIn Ver. 2.1

<210> 1

<211> 3255

<212> DNA

<213> mouse

<400> 1

ctcagcgagg ggaagggggaa ggaggcctgg atgactaaac ctgacagaaaa cgctggtggg 60  
aggctgggc gggcgccagt gccccgcgtag gtccttctcg acccgccagcc accacccgccc 120  
cggtgaccat gatagtgttt gtcagggtca actccagcta tggcttccca gtggagggtcg 180  
attctgacac cagcatcttg cagctcaagg aagtggttgc taagegacag ggggttccag 240  
ctgaccagct gctgtgtgatt tttgcgggaa aggagcttcc gaatcacctg acggttcaaa 300  
actgtgacct ggaacaacag agtattgtac acatagtaca gagaccacgg aggagaagtc 360  
atgaaacaaa tgcacatctgga ggggacgaac cccagagcac ctcagaggc tccatatggg 420  
agtccaggag cttgacacacg gtggacactgac gcagccatac cctgcgggtg gactctgtgg 480  
ggctggcggt cattctggac acagacagta agagggattc agaagcagcc agaggtccag 540  
ttaaaccac ctacaacacg ttttcatct actgcaaagg cccctgccac aaggtccagc 600  
ctggaaagct ccgagttcag tggacactgac gcaaaacaagc aaccctcacc ttggcccagg 660  
gccccatcttgc tgggacgat gtcttaattt caaacccggat gagttggtag tgccagtctc 720  
cagactgccc tggaaaccaga gctgaatttt tctttaaatg tggagcacac ccaacctcag 780  
acaaggacac gtcggtagct ttgaacctgaa tcaccagcaa cagggcgcagc atcccttgca 840  
tagcgtgcac agatgtcagg agccctgtcc tggcttcca gtgtacccac cgtcacgtga 900  
tctgtttggaa ctgtttccac ttgtattgtg tcacaagact caacgategg cagtttgcc 960  
acgatgcacca acttggctac tccctccgt gtgtacccac tccctgatta 1020  
aagagctcca tcacttcagg atccctggag aagagcagta cacttaggtac cagcagttatg 1080  
ggggcgagga atgcgtgtc caaatgggag gtgtgtgtg ccccccgtccct ggctgtggag 1140  
ctggactgtc acctgaacacg ggccagagga aagtccacctg cgaagggggc aacggccctgg 1200  
gtgtgggtt tggatctgc cgggactgtt aggaagcata ccatgaaggg gatgtcgact 1260  
cactgctcga accctcagga gccacttctc aggccctacag ggtggacaaa agagcccgctg 1320  
agcaagctcg ctgggaggag gcctccaaagg aaaccatcaa gaagaccacc aacccctgtc 1380  
ctcgctgcaaa cgtgccaatt gaaaaaaaaacg gaggatgtat gcacatgaag tggatctcagc 1440  
cccagtgcacca gctggagtgg tgctggaaact gtggctgtga gtggaaacgca gcctgcattgg 1500  
gagatcactg gtttgacgtg tagagagaga tggatctgg ccctggacgc acaacctcaa 1560  
gggaaactcc gaagattccctt accttcctta gccatttctt cttctcgatg catataagca 1620

cataaatgcg cacacacaaa cacaggctgc agattacaga agcagccct agatccttc 1680  
tagggcaccc acagaaaacc acagcacccg ctggccccag ggggaggagg cacttcagc 1740  
ctctggctca ctogaatgtc agagcttgc tgagggtgca ctttggttt ggattctgta 1800  
gaagccatga gtgagggtgg aagtgtttc caggggtgtt gcccacccct gggtaagtaa 1860  
cacctctgag gattctcaga agcacactt agatctgagg aacgctgctc tcatgttagta 1920  
atcatctatt cccaaagggc cccctgcagt agtcaaaact atttgtttat ccccccataat 1980  
cctatctta caaatggtgc ttagtgcattt acaacccctc tggactaa tcagcttatac 2040  
aaccaagtga gaaccttagga aagctaattt gatggcagac tgcttaaattc gcagggagga 2100  
ctcagaagcc aaacctactt ccgttcgttt cattatctgc aactttagaa agaaatgate 2160  
ttttttcccc cctgaaaaga taacaaagtc tgcaatttgg tttggaggtat tcctactgca 2220  
gcctggaagt ttagcttcac tggtaattt acagagaaaag tgcctataaa gggggcggtt 2280  
ttaagagaca atccccatgt gctgcgc当地 tgctaaacaac agggtaaaga aacacaatgt 2340  
ttatagaagg agcatccctc gaccatctga atgagagttt gctgacccc ttccaccaca 2400  
agtggggaca cctctgcata tctgctccct cctctgtgt taagccccag ggagcccat 2460  
ccacccagtg gtcctacaga cagggcaata cacacacacc aagatagct tcagatcaac 2520  
atgcatcaca ctcaagtgtt aatcttcaa ggtttctt tcttttctt gtttttatt 2580  
tggggctt tggcttttt ttttttttt tttgggtgtt gttttttttt cttttttttt 2640  
gcctagagct aaaaatcata tagaaaatgt gttatctgtt ggtgtgagga aaggccagct 2700  
ggcctaagtt cacacttttgc tccctgttcc cctagactcc acccagccag ctcccaaaat 2760  
gaaaagacca cctgtcaagc agcagtcagg agtctgtgtt caccatcac tttttttttt 2820  
ccatcattgt gcttgcctct gcctcttcc acacccgtgt gacgtaatcg cattgggaag 2880  
ccaggacaat gtttgcgtt ctgtttttgg taaaggact ccctgaagct ctgtggctct 2940  
ccagttatgtt cccttttctt tcctaaacaga tgcataatgtt ttcttcagaa tacaatagtg 3000  
attcttaaaa taacccaaaaa gacaggcatc cacagtgtgtt gacatgttccatc 3060  
attgtgtgag tggtaatagt gggataaaag tggatgtcag aagagtggaa atcaaaccctc 3120  
tgcaaaagcaaa tctttctt tctgtgaagt gtatagaa atacatgttccatc 3180  
tgggtgttacc cagactgtca atcaataaaag acccagactg tcaatgaaaa aaaaaaaaaa 3240  
aaaaaaaaaaaaaaa aaaaaa 3255

<210> 2  
<211> 1459  
<212> DNA  
<213> mouse

<400> 2  
cteacgggga ggaggccttgc gatgactaaa cctgacagaa acgctggtgg gaggctcggtt 60  
cggggcccaag tgcccggtt ggtccttcc gacccgcgc caccacccgc cccgtgacca 120  
tgatagtgtt tggtaatgttcc aactccagct atggcttccc agtggaggtc gattctgaca 180  
ccagcatctt gcagctcaag gaagtgggtt gtaagcgaca gggggttcca gctgaccaggc 240  
tgcgtgttat ttttgcggg aaggagctt cgaatcacct gacgggttccaa aactgtgacc 300  
tggaaacaaca gagtattgtt cacatgttcc agagaccacg gaggagaagt catgaaacaa 360  
atgcatctgg aggggacgaa ccccaagacgca cctcagaggc ctccatatgg gagtccaggaa 420  
gcttgacacg agtggacactg agcagccata ccctgcgggt ggactctgtt gggctggcg 480  
tcattcttgcgca cacagacagt aagagggtt cagaaggcgc cagagggttccaa gcatgttccaa 540  
ccacccatcaa cagcttttc atctactgttca aaggccccctg ccacaaggctc cagccctggaa 600  
agctccgagtt tcaatgttccatc acctgttccatc aagcaaccctt caccttggcc cagggcccat 660  
cttgcgtggaa cgtatgttccatc attccaaaccctt ggttggatgttccatc tgatgttccatc 720  
gccctggaaac cagactgttcaatgttccatc aatgttggatgttccatc acacccaaaccctt tcagacaaggc 780

acacgtcggt agctttgaac ctgatcacca gcaacaggcg cagcatccct tgcatagcgt 840  
gcacagatgt cagtcattt cctctgtcat ctgggtgcctc cgtgtggact cggcctcatc 900  
tccactgaac cttgttcttt aggactgtgc aataggtcgt cacctcttac tgagaacaag 960  
gcagcttctg gtctcttggt ttcccttgctt ccaacggcag cattgactgt acacccttca 1020  
gtccttaccaa ccccattacc tggttgattt ctttaccgct tagcttctcc aagatgccta 1080  
tttccacaca cagtttcttg tttccccat ccccccata gtttatgcgc atgagtaagc 1140  
accgcaccc tcatgtttgt gtttctgtata caagacttcc tgggatcccc gtttgcgc 1200  
tagaaatcccc tggaaactggg ttcaagtccat tatcttcaat agcctttttt aaaaatgtgagt 1260  
tcttgggctg gtgagatggc tcagtggtt agagcaccccg actgcttcc cgaagtccag 1320  
agttcaaaat cccagcaacc acatggtggc tcacacaaccat ccgtaaacaag atctgactcc 1380  
ctcttcttggt gtgtctgaag acagctacag tgtacttaca taaaataata aataaaatctt 1440  
aaaaaaaaaaaa aaaaaaaaaa 1459

<210> 3  
<211> 857  
<212> DNA  
<213> mouse

<400> 3  
ctcagatgac  
cgttagttct  
gttcaactcc  
caaggaagtg  
cgaaaaggag  
tgtacacata  
cgaaccccag  
cctgagcagc  
cagtaagagg  
tttcattcac  
tggcacctgc  
cttaattcca  
tgaattttc  
gaacctgatc  
tatgcgcatg

<210> 4  
<211> 464  
<212> PRT  
<213> mouse

<400> 4  
Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
1 5 10 15

Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
20 25 30

Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys

35                    40                    45

Glu Leu Pro Asn His Leu Thr Val Gln Asn Cys Asp Leu Glu Gln Gln  
50                    55                    60

Ser Ile Val His Ile Val Gln Arg Pro Arg Arg Arg Ser His Glu Thr  
65                    70                    75                    80

Asn Ala Ser Gly Gly Asp Glu Pro Gln Ser Thr Ser Glu Gly Ser Ile  
85                    90                    95

Trp Glu Ser Arg Ser Leu Thr Arg Val Asp Leu Ser Ser His Thr Leu  
100                  105                  110

Pro Val Asp Ser Val Gly Leu Ala Val Ile Leu Asp Thr Asp Ser Lys  
115                  120                  125

Arg Asp Ser Glu Ala Ala Arg Gly Pro Val Lys Pro Thr Tyr Asn Ser  
130                  135                  140

Phe Phe Ile Tyr Cys Lys Gly Pro Cys His Lys Val Gln Pro Gly Lys  
145                  150                  155                  160

Leu Arg Val Gln Cys Gly Thr Cys Lys Gln Ala Thr Leu Thr Leu Ala  
165                  170                  175

Gln Gly Pro Ser Cys Trp Asp Asp Val Leu Ile Pro Asn Arg Met Ser  
180                  185                  190

Gly Glu Cys Gln Ser Pro Asp Cys Pro Gly Thr Arg Ala Glu Phe Phe  
195                  200                  205

Phe Lys Cys Gly Ala His Pro Thr Ser Asp Lys Asp Thr Ser Val Ala  
210                  215                  220

Leu Asn Leu Ile Thr Ser Asn Arg Arg Ser Ile Pro Cys Ile Ala Cys  
225                  230                  235                  240

Thr Asp Val Arg Ser Pro Val Leu Val Phe Gln Cys Asn His Arg His  
245                  250                  255

Val Ile Cys Leu Asp Cys Phe His Leu Tyr Cys Val Thr Arg Leu Asn  
260                  265                  270

Asp Arg Gln Phe Val His Asp Ala Gln Leu Gly Tyr Ser Leu Pro Cys  
275                  280                  285

Val Ala Gly Cys Pro Asn Ser Leu Ile Lys Glu Leu His His Phe Arg

290                    295                    300

Ile Leu Gly Glu Glu Gln Tyr Thr Arg Tyr Gln Gln Tyr Gly Ala Glu  
305                    310                    315                    320

Glu Cys Val Leu Gln Met Gly Gly Val Leu Cys Pro Arg Pro Gly Cys  
325                    330                    335

Gly Ala Gly Leu Leu Pro Glu Gln Gly Gln Arg Lys Val Thr Cys Glu  
340                    345                    350

Gly Gly Asn Gly Leu Gly Cys Gly Phe Val Phe Cys Arg Asp Cys Lys  
355                    360                    365

Glu Ala Tyr His Glu Gly Asp Cys Asp Ser Leu Leu Glu Pro Ser Gly  
370                    375                    380

Ala Thr Ser Gln Ala Tyr Arg Val Asp Lys Arg Ala Ala Glu Gln Ala  
385                    390                    395                    400

Arg Trp Glu Glu Ala Ser Lys Glu Thr Ile Lys Lys Thr Thr Lys Pro  
405                    410                    415

Cys Pro Arg Cys Asn Val Pro Ile Glu Lys Asn Gly Gly Cys Met His  
420                    425                    430

Met Lys Cys Pro Gln Pro Gln Cys Lys Leu Glu Trp Cys Trp Asn Cys  
435                    440                    445

Gly Cys Glu Trp Asn Arg Ala Cys Met Gly Asp His Trp Phe Asp Val  
450                    455                    460

<210> 5  
<211> 262  
<212> PRT  
<213> mouse

<400> 5  
Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
1                    5                    10                    15

Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
20                    25                    30

Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
35 40 45

Glu Leu Pro Asn His Leu Thr Val Gln Asn Cys Asp Leu Glu Gln Gln  
50 55 60

Ser Ile Val His Ile Val Gln Arg Pro Arg Arg Arg Ser His Glu Thr  
65 70 75 80

Asn Ala Ser Gly Gly Asp Glu Pro Gln Ser Thr Ser Glu Gly Ser Ile  
85 90 95

Trp Glu Ser Arg Ser Leu Thr Arg Val Asp Leu Ser Ser His Thr Leu  
100 105 110

Pro Val Asp Ser Val Gly Leu Ala Val Ile Leu Asp Thr Asp Ser Lys  
115 120 125

Arg Asp Ser Glu Ala Ala Arg Gly Pro Ala Val Lys Pro Thr Tyr Asn  
130 135 140

Ser Phe Phe Ile Tyr Cys Lys Gly Pro Cys His Lys Val Gln Pro Gly  
145 150 155 160

Lys Leu Arg Val Gln Cys Gly Thr Cys Lys Gln Ala Thr Leu Thr Leu  
165 170 175

Ala Gln Gly Pro Ser Cys Trp Asp Asp Val Leu Ile Pro Asn Arg Met  
180 185 190

Ser Gly Glu Cys Gln Ser Pro Asp Cys Pro Gly Thr Arg Ala Glu Phe  
195 200 205

Phe Phe Lys Cys Gly Ala His Pro Thr Ser Asp Lys Asp Thr Ser Val  
210 215 220

Ala Leu Asn Leu Ile Thr Ser Asn Arg Arg Ser Ile Pro Cys Ile Ala  
225 230 235 240

Cys Thr Asp Val Ser His Leu Pro Leu Ser Ser Gly Ala Ser Val Trp  
245 250 255

Thr Arg Pro His Leu His  
260

<210> 6

<211> 250

<212> PRT  
<213> mouse

&lt;400&gt; 6

Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
1 5 10 15

Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
20 25 30

Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
35 40 45

Glu Leu Pro Asn His Leu Thr Val Gln Asn Cys Asp Leu Glu Gln Gln  
50 55 60

Ser Ile Val His Ile Val Gln Arg Pro Arg Arg Arg Ser His Glu Thr  
65 70 75 80

Asn Ala Ser Gly Gly Asp Glu Pro Gln Ser Thr Ser Glu Gly Ser Ile  
85 90 95

Trp Glu Ser Arg Ser Leu Thr Arg Val Asp Leu Ser Ser His Thr Leu  
100 105 110

Pro Val Asp Ser Val Gly Leu Ala Val Ile Leu Asp Thr Asp Ser Lys  
115 120 125

Arg Asp Ser Glu Ala Ala Arg Gly Pro Ala Val Lys Pro Thr Tyr Asn  
130 135 140

Ser Phe Phe Ile Tyr Cys Lys Gly Pro Cys His Lys Val Gln Pro Gly  
145 150 155 160

Lys Leu Arg Val Gln Cys Gly Thr Cys Lys Gln Ala Thr Leu Thr Leu  
165 170 175

Ala Gln Gly Pro Ser Cys Trp Asp Asp Val Leu Ile Pro Asn Arg Met  
180 185 190

Ser Gly Glu Cys Gln Ser Pro Asp Cys Pro Gly Thr Arg Ala Glu Phe  
195 200 205

Phe Phe Lys Cys Gly Ala His Pro Thr Ser Asp Lys Asp Thr Ser Val  
210 215 220

Ala Leu Asn Leu Ile Thr Ser Asn Arg Arg Ser Ile Pro Cys Ile Ala  
225 230 235 240

Cys Thr Asp Val Arg Phe Met Arg Met Ser  
245                    250

<210> 7  
<211> 3014  
<212> DNA  
<213> mouse

<400> 7  
ctcagcgagg ggaaggggga ggaggcctgg atgactaaac ctgacagaaaa cgctgggtggg 60  
aggctcgggc gggcgccagt gcccgcgtag gtccttctcg acccgccagcc accacccgccc 120  
cggtgaccat gatagtgttt gtcaggttca actccagcta tggcttccca gtggagggtcg 180  
attctgacac cagcatctt cagctcaagg aagtgggtgc taagcgacag ggggttccag 240  
ctgaccagct gcgtgtgatt tttgccggga aggagcttcc gaatcacctg acggttcaat 300  
taaaccacc tacaaacagct ttttcatctt ctgcaaaggc ccctgccaca aggtccagcc 360  
tggaaagctc cgagttcagt gtggcacctg caaacaagca accctcacct tggcccaggg 420  
cccatcttgc tgggacgatg tcttaattcc aaaccggatg agtggtgagt gccagtctcc 480  
agactgcct ggaaccagag ctgaattttt cttaaatgt ggagcacacc caacctcaga 540  
caaggacacg tcggtagctt tgaacctgat caccagcaac aggccgcagca tcccttgcatt 600  
agcgtgcaca gatgtcagga gcccgtctt ggtcttccag tctaaccacc gtcacgtgat 660  
ctgtttggac tgtttccact tgtattgtgt cacaagactc aacgatggc agtttgtcca 720  
cgatgctcaa ctggctact ccctgcccgtg tgttagctggc tgtcccaact ccctgattaa 780  
agagctccat cacttcagga tcttggaga agagcagtac actaggtacc agcagtatgg 840  
ggccgagggaa tgcgtgctgc aaatgggagg tgtgctgtgc ccccgccctg gctgtggagc 900  
tggactgcta cctgaacagg gccagagggaa agtcacctgc gaagggggca acggcctggg 960  
ctgcgggttt gtttctgcc gggactgtaa ggaagcatac catgaagggg attgctgactc 1020  
actgctgaa ccctcaggag ccacttctca ggcctacagg gtggacaaaa gagccgctga 1080  
gcaagctcgc tggaggagg cctccaagga aaccatcaag aagaccacca agccttgc 1140  
tcgctgcaac gtgccaattt aaaaaaacgg aggatgtatg cacatgaagt gtcctcagcc 1200  
ccagtgcacg ctggagtggt gctggaaactg tggctgtgag tggacccggag cctgcattgg 1260  
agatcactgg tttgacgtgt agagagagat gtcacccgttgc cctggacgca caacctcaag 1320  
ggaaaactccg aagatctca ccttccttag ccatttcttc ttctcgatgc atataagcac 1380  
ataaaatgcgc acacacaaac acaggctgca gattacagaa gcagccccata gatectttct 1440  
agggcaccca cagaaaaacca cagcacccgc tggccccagg gggaggaggc actttcagcc 1500  
tctggctcac tcgaatgtca gagcttagat gaggtgcac ctttggtttg gattctgttag 1560  
aagccatgag tgaggtggga agtgtttcc aggggttggc ccacgccccgt ggtaagtaac 1620  
acctctgagg attctcagaa gcacacttga gatctgagga acgctgctct catgtagtaa 1680  
tcatcttatcc ccaaaggccc ccctgcagta gtcaaaacta tttgtttatc ccccccaatc 1740  
ctatcttac aaatgggtct gatgagatta caaccctctt gtgtactaat cagcttataca 1800  
accaagttag aaccttaggaa agctaattgg atggcagact gcttaaatcg cagggaggac 1860  
tcagaagccaa aacctacttc cgttcggttc attatctgca actttagaaaa gaaatgatct 1920  
ttttttcccc ctgaaaagat aacaaagtct gcaattttggt ttggagtatt cctactgcag 1980  
cctggaaaggtagcttact gtgaatttaa cagagaaagt gcctataaag gggcggtttt 2040  
taagagacaa tcccattatgt ctgcgcataat gctaacaaca gggtcaagaa acacaatgtt 2100  
tatagaagga gcatccctcg accatctgaa tgagagtatg cctgaccctt tccaccacaa 2160  
gtggggacac ctctgcataat ctgctccctc ctctgctgtt aagccccagg gagccccatc 2220

cacccagttg tcctacagac agggcaatac acacacacca agatagcctt cagatcaaca 2280  
 tgcacacac tcaagtgtta atctttcaag gttttctttt cttttcctg ttttttattt 2340  
 gttttcttt tgctttttt tttttttt ttgggtggg tggggctacc aaacttgagg 2400  
 ccttagagcta aaaatcatat agaaaatgtt ttatcttgcgt gtgtgaggaa aggccagctg 2460  
 gcctaagttc acactttgt cccagtgccc cttagactcca cccagccagc tccccaaatg 2520  
 aaaagaccac ctgtcaagca gcagtcagga gtctgatgtc acccatcaact atttttttc 2580  
 catcattgtg cttgcctctg cttccttcca caccgtgtg acgtaatcg 2640  
 caggacaatg tttgtgttc tgctttgggt aaagggactc cctgaagctc tgtggctctc 2700  
 cagttatggtc cttttcctt cctaacagat gcatatgttt tcttcagaat acaatagtga 2760  
 ttcttaaaat aacccaaaag acaggcatcc acagtgtgtg agcatgaatc acagectgca 2820  
 ttgtgtgagt gtgaatagtg ggataaaaat ggatgtcaga agatggaaa tcaaacctct 2880  
 gcaaagcaat ctttctttt ctgtgaagtg tattaagaaa tacctgaagt ctgtgtgt 2940  
 ggtggtaccc agactgtcaa tcaataaaga cccagactgt caatgaaaaa aaaaaaaaaa 3000  
 aaaaaaaaaa aaaa 3014

<210> 8  
 <211> 2895  
 <212> DNA  
 <213> mouse

<400> 8  
 ctcagcgagg ggaagggggga ggaggcctgg atgactaaac ctgacagaaaa cgctgggtggg 60  
 aggctcgggc gggcgccagt gcccgegtag gtccttcctcg acccgccagcc accacccggcc 120  
 cggtgaccat gatagtgttt gtcaggttca actccageta tggcttccca gtggaggtcg 180  
 attctgacac cagcatctt cagctcaagg aagtgggtgc taagcgcacag ggggttccag 240  
 ctgaccagct gcgtgtgatt tttggggga aggagcttcc gaatcacctg acgggttcaag 300  
 gcccattttt ctgggacgat gtcttaattt caaaccggat gagtgggtgag tgccagtc 360  
 cagactgccccc tggaaccaga gctgaatttt tctttaatg tggagcacac ccaacctcag 420  
 acaaggacac gtcggtagct ttgaacctga tcaccagcaa cagggcgacg atcccttgc 480  
 tagcgtgcac agatgtcagg agccctgtcc tggcttccca gtgttaaccac cgteacgtga 540  
 tctgtttggg ctgtttccac ttgtattgtg tcacaagact caacgatcg cagtttgc 600  
 acgatgctca acttgetac tccctgcgt gtgtagctgg ctgttccaaac tccctgatta 660  
 aagagcttcca tcacttcagg atccctggag aagagcagta cactaggta cagcagtatg 720  
 gggccgagga atgcgtgtg caaatggag gtgtgtgtg ccccegttctt ggctgtggag 780  
 ctggactgtc acctgaacag gcccagagga aagtccatcg cgaaggggggc aacggccctgg 840  
 gctgggggt tgtttctgc cgggactgtc aggaagcata ccatgaaggg gatttgcact 900  
 cactgctcga accctcagga gccacttcctc aggcttacag ggtggacaaa agagccgtg 960  
 agcaagctcg ctgggaggag gccttcaagg aaaccatcaa gaagaccacc aagccttgc 1020  
 ctcgctgcaa cgttccaaatt gaaaaaaaaacg gaggatgtat gcacatgaag tgccttcagc 1080  
 cccagtgc aa gctggagtgg tgctgaaact gtggctgtga gtggacccga gctgcattgg 1140  
 gagatcactg gtttgcgtg tagagagaga tgctacttgg ccctggacgc acaacctcaa 1200  
 gggaaactcc gaagatctt accttcctt gccattttt cttctegatg catataagca 1260  
 cataaatgcg cacacacaaa cacaggctgc agattacaga agcagccccctt agatcccttc 1320  
 tagggcaccc acagaaaaacc acagcacccg ctggccccag ggggaggagg cactttcage 1380  
 ctctggctca ctcgaatgtc agagcttgcg tgaggggtgca cctttgggtt ggatttgc 1440  
 gaagccatga gtgaggtggg aagtgtttt cagggtgtt gccacgccccctt gggtaagtaa 1500  
 cacctctgag gatttgcaga agcacactt gatctgagg aacgctgctc tcatgttagta 1560  
 atcatctatt cccaaaggc cccctgcagt agtccaaact atttgtttat ccccccaat 1620

cctatctta caaatgggtgc tgatgagatt acaacccctc tgcgtactaa tcagcttatac 1680  
 aaccaagtga gaaccttagga aagctaattg gatggcagac tgcttaaatac gcagggagga 1740  
 ctcagaagcc aaacctactt ccgttcgttt cattatctgc aacttttagaa agaaatgatc 1800  
 ttttttcccc cctgaaaaga taaccaaagtc tgcaatttgg tttggaggtat tcctactgca 1860  
 gcctggaagt tttagttcac tgcgtattt acagagaaaag tgcctataaaa gggggcggtt 1920  
 ttaagagaca atcccatgtat gctgcgcacaa tgctaacaaac agggtcaaga aacacaatgt 1980  
 ttatagaagg agcataccctc gaccatctga atgagaggtat gcctgacccc ttccaccaca 2040  
 agtggggaca cctctgcata tctgtccct cctctgtgt taagccccag ggagccccat 2100  
 ccacccagtg gtcctacaga cagggcaata cacacacacc aagatagct tcagatcaac 2160  
 atgcatacaca ctcaagtgtt aatcttcaa gtttttctt ttttttctt gtttttatt 2220  
 ttttttgctt ttgctttttt tttttttttt tttgggtgtg gtggggctac caaacttgag 2280  
 gcctagagct aaaaatcata tagaaatgtat gttatettgt ggtgtgagga aaggccagct 2340  
 ggcctaagtt cacacttttgc tcccagtggc cctagactcc acccagocag ctcccaaaat 2400  
 gaaaagacca cctgtcaagc agcagtcagg agtctgtatgt cacccatcac tttttttttt 2460  
 ccatcattgt gcttgcctct gcctccttcc acaccgtgt gacgtaatcg cattgggaag 2520  
 ccaggacaat gtttgcgtt ctgtttggg taaagggact ccctgaagct ctgtggctct 2580  
 ccagttatgtt ccctttccct tcctaacaga tgcataatgtt ttcttcagaa tacaatagt 2640  
 attcttaaaa taacccaaaaa gacaggcatc cacagtgtgt gagcatgaat cacagcctgc 2700  
 attgtgtgag tgtgaatagt gggataaaag tggatgtcag aagagtggaa atcaaacccctc 2760  
 tgcaagcaa tctttcttctt tctgtgaagt gtattaagaa atacctgaag tctgtgtgt 2820  
 tggtggtacc cagactgtca atcaataaaag acccagactg tcaatgaaaa aaaaaaaaaa 2880  
 aaaaaaaaaaaa aaaaaa 2895

<210> 9  
<211> 2558  
<212> DNA  
<213> mouse

<400> 9

ctcagcgagg ggaaggggga ggagggctgg atgactaaac ctgacagaaaa cgctgggtggg 60  
 aggctcgggc gggcgccagt gcccgcgtag gtccttcctcg acccgccagcc accacccggcc 120  
 cggtgaccat gatagtgttt gtcaggttca actccagctta tggcttccca gtggaggtcg 180  
 attctgacac cagcatcttgc cagctcaagg aagtgggtgc taagcgacag ggggttccag 240  
 ctgaccagct gcgtgtgatt tttggggaa aggagcttcc gaatcaccttgc acgggttcaac 300  
 tggctgtccc aactccctga tttaagagct ccatacttc aggatccttgc gagaagagca 360  
 gtacactagg taccagcgt atggggccga ggaatgcgtg ctgcaaatgg gaggtgtgt 420  
 gtgccccctgt cctggctgtg gagctggact gctacctgaa cagggccaga gaaaagtcac 480  
 ctgcgaaggg ggcaacggcc tgggtgcgg gtttgcgttgc tgccggact gtaaggaagc 540  
 ataccatgaa ggggattgcg actcaactgtc cgaacccctca ggagccactt ctcaggccata 600  
 cagggtggac aaaagagccg ctgagcaagc tcgctggag gaggccctcca aggaaaccat 660  
 caagaagacc accaagccctt gtcctcgctg caacgtgcac attgaaaaaa acggaggatg 720  
 tatgcacatg aagtgttcc agcccccagtgc caagctggag tgggtgcgttgc actgtggctg 780  
 tgagtggAAC cgaggcctgc tgggagatca ctgggttgcgttgc tgtagagag agatgtcact 840  
 tggccctggc cgcacaaacctt caagggaaac tccgaagatt cctaccccttcc ttagccattt 900  
 cttcttcgtt atgcataataa gcacataat ggcacacacaa accacacaggc tgcagattac 960  
 agaagcagcc cctagatctt ttcttagggca cccacagaaaa accacagcac ccgcgtggccc 1020  
 cagggggagg aggcaacttgc agcctctggc tcactcgaat gtcagagctt agatgagggt 1080  
 gcaccccttgg tttggattct gtagaagccca tgagtggat gggaaatgtt ttccagggtt 1140

gttgcgccgc cctgggtaag taacacctct gaggattctc agaagcacac ttgagatctg 1200  
aggaacgctg ctctcatgt aatacatactt attcccaaag ggccccctgc agtagtcaaa 1260  
actatttgtt tatcccccca aatcctatct ttacaaatgg tgctgtatgattacaaccc 1320  
ctctgtgtac taatcagctt atcaaccaag tgagaaccta ggaaagctaa ttggatggca 1380  
gactgcttaa atcgcaggga ggactcagaa gccaaaccta cttccgttcg tttcattatc 1440  
tgcaactta gaaagaaaatg atctttttt cccccctgaaa agataacaaa gtctgcaatt 1500  
tggtttggag tattectact gcagccttgg a gtttagctt cactgtgaat ttaacagaga 1560  
aagtgcctat aaagggggcg ttttaagag acaatcccattt gatgctgcgc caatgctaac 1620  
aacagggtca agaaaacacaa tgtttataga aggagcatcc ctcgaccatc tgaatgagag 1680  
tatgcctgac cccttccacc acaagtgggg acacctetgc atatctgtc ctcctctgc 1740  
tgttaagccc cagggagccc catccaccca gtgggtctac agacagggca atacacacac 1800  
accaagatag cttcagatc aacatgcattt acactcaagt gttaatctttt caaggttttc 1860  
ttttttttt cctgtttttt atttgtttt cttttgtctttt tttttttttt tttttttttt 1920  
gtgggtgggc taccaaactt gaggcctaga gctaaaaatc atatagaaat gatgttatct 1980  
tgtggtgtga ggaaaggcca gctggctaa gttcacactt ttgtcccaagt gcccctagac 2040  
tccacccaggc cagttcccaa aatgaaaaga ccacctgtca agcagcagtc aggagtctga 2100  
tgtcacccat cactatttt ttccatcat tggcttgc tctgccttcc tccacacccg 2160  
tgtgacgtaa tcgcattggg aagccaggac aatgtttgtt gttctgtctt gggtaaagg 2220  
actccctgaa gctctgtggc tctccagttt ggtccctttt cttcttaac agatgcata 2280  
gttttcttca gaatacataa gtgattctt aataaaccctt aaagacagggc atccacagtg 2340  
tgtgagcatg aatcacagcc tgcattgtgt gagtgtgaat agtggataa aagtggatgt 2400  
cagaagagtg gaaatcaaac ctctgcaaag caatcttctt cttctgtga agtgtattaa 2460  
gaaataacctg aagtctgtgt gtgtgggtt acccagactg tcaatcaata aagacccaga 2520  
ctgtcaatga aaaaaaaaaaaaaaaa aaaaaaaaaaaaaaaa aaaaaaaaaaaaaaaa 2558

```
<210> 10  
<211> 3136  
<212> DNA  
<213> mouse
```

<400> 10  
ctcagcgagg  
aggctcgggc  
cggtgaccat  
attctgacac  
ctgaccagct  
actgtgacct  
atgaaaacaaa  
agtccaggag  
ggctggcggt  
ggccccatctt  
ccagactgcc  
gacaaggaca  
atacgctgca  
atctgtttgg  
cacgatgtct  
aaagagctcc  
ggggcccgagg

gctggactgc tacctgaaca gggccagagg aaagtcaacct gcgaagggggg caacggcctg 1080  
 ggctgcgggt ttgttttctg cccggactgt aagaagcat accatgaagg ggattgcgac 1140  
 tcactgctcg aaccctcagg agccacttct cagccctaca gggtgacaa aagageegct 1200  
 gagcaagctc gctgggagga ggcctccaag gaaaccatca agaagaccac caagccttgt 1260  
 cctcgctgca acgtgcata taaaaaaaac ggaggatgtc tgccatgaa gtgcctcag 1320  
 ccccagtgc a gctggagtg gtgctggAAC tggctgtc agtggAACCG agctgcgt 1380  
 ggagatcaact gtttgcgt gtagagagag atgtcaacttgc gcccggacg cacaacctca 1440  
 agggaaactc cgaagattcc taccttcctt agccatttct tcttcgtat gcatataagc 1500  
 acataaatgc gcacacacaa acacaggtcg cagattacag aagcagcccc tagatecttt 1560  
 cttagggcacc cacagaaaac cacagcaccc gctggccca gggggaggag gcactttcag 1620  
 cctctggctc actcgaatgt cagagcttag atgagggtgc acctttgggt tggattctgt 1680  
 agaagccatg agtgaggtgg gaagtgtttt ccagggtgt tgccacgccc tggtaagta 1740  
 acacctctga ggatttcag aagcacaactt gagatctgag gaacgtgtct ctcatgttagt 1800  
 aatcatctat tcccaaaggc cccctgcag tagtcaaaac tatttggta tccccccaaa 1860  
 tcctatctt acaaatggtg ctgatgagat tacaacccct ctgtgtacta atcagcttat 1920  
 caaccaagtg agaacctagg aaagctaatt ggatggcaga ctgtttaat cgcaaggagg 1980  
 actcagaagc caaacctact tccgttgcgtt tcattatctg caactttaga aagaaatgtat 2040  
 ctttttttcc ccctgaaaag ataacaaagt ctgcaatttgc gtttggagta ttctactgc 2100  
 agcctggaaag tttagettca ctgtgaattt aacagagaaa gtgcctataa agggggcggt 2160  
 ttttaagagac aatccccatga tgctgcgcca atgtaacaa cagggtcaag aaacacaatg 2220  
 tttatagaag gagcattccct cgaccatctg aatgagagta tgccgtaccc ttccaccac 2280  
 aagtggggac acctctgcattt atctgctccc tcctctgtt ttaagccccca gggagccccca 2340  
 tccacccagt ggtcttacag acagggcaat acacacacac caagatagcc ttcatgtcaa 2400  
 catgcattcac actcaagtgt taatcttca aggtttttt ttcttttcc ttttttttat 2460  
 ttgttttgc tttgtttttt tttttttttt ttttgggtgtt ggtggggcta ccaaacttga 2520  
 ggccttagagc taaaaatcat atagaaatga ttttatgtt tgggtgtgagg aaaggccagc 2580  
 tggtttaagt tcacactttt gtcccagtgg cccttagactc caccgcacca gctcccaaaa 2640  
 tggaaagacc acctgtcaag cagcagtcag gatgtgtatgc tcacccatca ctatttttt 2700  
 tccatcatgg tgcttgcctc tgcccttcc cacacccgtt tgacgtatc gcattggaa 2760  
 gccaggacaa tttttgtgt tctgttttgg gtaaaggac tccctgaagc tctgtggctc 2820  
 tccagtatgg tcccttttcc tcccttaacag atgcatatgt ttttttcaga atacaatagt 2880  
 gatttttaaa ataacccaaa agacaggcat ccacagtgtt tgagcatgaa tcacagcctg 2940  
 cattgtgtga gtgtgaatag tggataaaa gtggatgtca gaagagtggaa aatcaaaccct 3000  
 ctgcaaaagca atctttctt ttctgtgaag tgtattaaga aatacctgaa gtctgtgtt 3060  
 gtgggtgtac ccagactgtc aatcaataaa gaccagact gtcaatgaaa aaaaaaaaaa 3120  
 aaaaaaaaaa aaaaaaa 3136

<210> 11  
 <211> 3170  
 <212> DNA  
 <213> mouse

<400> 11  
 ctcagcgagg ggaagggggg ggaggcctgg atgactaaac ctgacagaaa cgctgggtgg 60  
 aggctcgccgc gggcgccagt gcccgcgtag gtccctctcg acccgccagcc accacccgccc 120  
 cggtgaccat gatgtgtttt gtccagggtca actccagctt tggcttccca gtggaggtcg 180  
 attctgacac cagcatcttgc cagctcaagg aagtgggtgc taagcgcacag ggggttccag 240  
 ctgaccagct gctgtgttatttttggaa aggagcttccca gaatcacctg acggttcaaaa 300

actgtgacat ggaacaacag agtattgtac acatagtaca gagaccacgg aggagaagtc 360  
atgaaacaaa tgcatacttggaa ggggacaaac cccagagcac ctcagaggc tccatatggg 420  
agtccaggag cttgacacga gtggacctga gcagccatac cctgcccgtg gactctgtgg 480  
ggctggcggt cattctggac acagacagta agagggattc agaagcagcc agaggccat 540  
ttaaaccac ctacaacagc ttttcatct actgcaaaagg cccctgccac aaggccat 600  
ctggaaagct ccgagtttagt tgtagccac gcaaacaagc aaccctcacc ttggcccaga 660  
attttcttt aaatgtggag cacaccaac ctcagacaag gacacgtcg tagetttgaa 720  
cctgatcacc agcaacaggc gcagcatccc ttgcatagcg tgcacagatg tcaggagccc 780  
tgtctggtc ttccagtgtt accacgtca cgtatctgt ttggactgtt tccacttgta 840  
ttgtgtcaca agactcaacg atcggcagtt tgccacatg gtcacttg gctactccct 900  
gccgtgtgtt gctggctgtc ccaactccct gattaaagag ctccatcaact tcaggatcc 960  
tggagaagag cagtacacta ggtaccagca gtagggggcc gaggaatgcg tgctgcaaat 1020  
gggaggtgtg ctgtgcccccc gtcctggctg tgtagctggta ctgctacctg aacaggccca 1080  
gaggaaagtc acctgcgaag gggcaacgg cttggctgc gggtttggg tctgcccggg 1140  
ctgtaaaggaa gcataccatg aaggggattt cgactcaactg ctcgaaccct caggagccac 1200  
ttctcaggcc tacagggtgg acaaaagagc cgctgagca gtcgctggg aggaggccct 1260  
caaggaaacc atcaagaaga ccaccaagcc ttgtctcg tgcacatgc caattgaaaa 1320  
aaacggagga tgtatgcaca tgaagtgtcc tcagccccag tgcaagctgg agtggtgctg 1380  
gaactgtggc tggtagtgg accgagccctg catggagat cactggttt acgtgttagag 1440  
agagatgtca cttggccctg gacgcacaaac ctcaaggaa actccgaaactt ttcctacett 1500  
ccttagccat ttcttcttct cgtatcatat aagcacataa atgcgcacac acaaacacag 1560  
gctgcagatt acagaagcag cccctagatc cttcttaggg caccacaga aaaccacagc 1620  
acccgctggc cccagggggg ggaggcactt tcagccctgc gtcactcgat atgtcagagc 1680  
tttagatgagg gtgcacccctt ggtttggatt ctgtagaagg catgagtgag gtggaaagtg 1740  
ttttccaggg ttgttgccac gcccctggta agtaacacact ctgaggattc tcaagacac 1800  
acttgagatc tgaggaacgc tgcctcatg tagtaatcat ctatccccaa agggccccct 1860  
gcagtagtca aaactatttgc tttatccccca caaatcttat ctttacaaat ggtgctgatg 1920  
agattacaac ccctctgtgt actaatcaggc ttatcaacca agtgagaacc taggaaagct 1980  
aattggatgg cagactgctt aaatgcagg gaggactca gaggccaaacc tacttccgtt 2040  
cgccccat tctgcacactt tagaaagaaa tgcattttttt ttccccctga aaagataaca 2100  
aagtctgca tttggtttgg agtattccctt ctgcagccctg gaagtttagc ttcactgtga 2160  
attnaacaga gaaagtgcct ataaagggggg cgtttttaag agacaatccc atgatgtgc 2220  
gccaatgcta acaacagggt caagaaacac aatgtttata gaaggagcat ccctcgacca 2280  
tctgaatgag agtatgcctg acccccttcca ccacaagtgg ggacacccctt gcatatctgc 2340  
tccctctct cgtgttaagc cccagggggc cccatccacc cagtggccct acagacaggg 2400  
caatacacac acaccaagat agccttcaga tcaacatgc tcaactcaa gtgttaatct 2460  
ttcaaggttt tcttttcttt ttccctgttt ttatgttt tgctttgtt tttttttttt 2520  
ttttttttgg tgggtgggg gctaccaaactt tgaggccata gagctaaaaa tcatatagaa 2580  
atgatgttat ctgtgggtt gaggaaaggc cagctggccct aagttcacac ttttgcctca 2640  
gtggccctag actccaccca gccagctccc aaaatgaaaaa gaccacctgt caagcagcag 2700  
tcaggagtct gatgtcaccc atcactattt ttttccatc attgtgttttgc cctctgcctc 2760  
cttccacacc cgtgtgacgt aatcgcattt ggaagccagg acaatgttttgc tgggtctgt 2820  
ttgggtaaag ggactccctg aagctctgtg gctctccagt atggccctt tcccttccta 2880  
acagatgcac atgttttctt cagaatacaa tagtgattct taaaataacc caaaagacag 2940  
gcacccacag tggtagc tgaatcaccag cctgcattgt gtgagtgatg atagtggtt 3000  
aaaatggat gtcagaagag tggaaatcaa acctctgc tcaatctttt ctctttctgt 3060  
gaagtgtatt aagaaatacc tgaagtctgt gtgtgtgggt gtaccagac tgcataatcaa 3120  
taaagaccca gactgtcaat gaaaaaaaaaaaaaaa aaaaaaaaaaaa 3170

<210> 12  
<211> 2918  
<212> DNA  
<213> mouse

<400> 12

ctcagcgagg ggaaggggga ggaggcctgg atgactaaac ctgacagaaaa cgctggtggg 60  
aggctgggc gggcgcagt gcccgcgtag gtccttctcg acccgccagcc accacccggcc 120  
cggtgaccat gatagtgttt gtcaggttca actccagcta tggcttccca gtggaggtcg 180  
attctgacac cagcatcttgc agctcaagg aagtgggtgc taagcgacag ggggttccag 240  
ctgaccagct gcgtgtgatt tttgccggga aggagcttcc gaatcacctg acggttcaaa 300  
actgtgacac ggaacaacag agtattgtac acatagtaca gagaccacgg aggagaagtc 360  
atgaaacaaa tgcatctgga ggggacgaac cccagagcac ctcagaggc tccatatggg 420  
agtccaggag cttgacacga gtggacactga gcagccatac cctgccggtg gactctgtgg 480  
ggctggcggt cattctggac acagacagta agagggattc agaagcagcc agaggtccag 540  
ttaaacccac ctacaacacgc ttttcatct actgcaaagg cccctgcac aaggtccagc 600  
ctggaaagct ccgagtttag tggcacact gcaaaacaagg aaccctcacc ttggcccagc 660  
tggctgtccc aactccctga ttaaagagct ccatcacttc aggatccttgc gagaagagca 720  
gtacactagg taccagcgt atggggccga ggaatgcgtg ctgcaaatgg gaggtgtgct 780  
gtgccccctgt cctggctgtg gagctggact gctacctgaa cagggccaga gggaaagtca 840  
ctgcgaaggg ggcaacggcc tgggctgccc gtttgcggact tgccggact gtaaggaagc 900  
ataccatgaa ggggattgcg actcaactgtc cgaaccctca ggagccactt ctcaggccta 960  
cagggtggac aaaagagccg ctgagcaacgc tcgctggag gaggcctcca aggaaaccat 1020  
caagaagacc accaaggcctt gtcctcgctg caacgtgcca attgaaaaaaaa acggaggatg 1080  
tatgcacatg aagtgtccctc agccccagtg caagctggag tggtgctggact gactgtggctg 1140  
tgagtggAAC ccagccctgca tgggagatca ctgggttgac gtgttagagag agatgtca 1200  
tggcccttggc cgcacaacctt caagggaaac tccgaagatt cctaccccttcc ttageccattt 1260  
cttcttctcg atgcataataa gcacataaaat ggcacacac aaacacaggc tgcaagattac 1320  
agaagcagcc cctagatcct ttcttagggca cccacagaaaa accacagcac ccgctggccc 1380  
cagggggagg aggcaacttgc agcctctggc tcactcgaat gtcagagctt agatgagggt 1440  
gcaccccttgg tttggattct gtagaagcca tgagtggact gggaaagtgtt ttccagggtt 1500  
gttgcacgc cctgggttaag taacacetct gaggattctc agaagcacac tttagatctg 1560  
aggaacgctg ctctcatgtt gtaatcatctt attccaaag ggccccctgc agtagtcaaa 1620  
actatattgtt tatcccccca aatccatctt ttacaatgg tgctgtatgatgattacaaccc 1680  
ctctgtgtac taatcagctt atcaaccaag tgagaaccta ggaaagctaa ttggatggca 1740  
gactgcttaa atcgcaggga ggactcagaa gccaaaccta cttccgttgc tttcattatc 1800  
tgcaacttta gaaagaaatg atctttttt cccctgaaa agataacaaa gtctgcaatt 1860  
tggtttggag tattctact gcagcctggc agtttagctt cactgtaat ttaacagaga 1920  
aagtgcctat aaagggggcg ttttaagag acaatccccat gatgctgcgc caatgctaac 1980  
aacagggtca agaaacacaa tggatataaga aggacatcc ctcgaccatc tgaatgagag 2040  
tatgcctgac cccttccacc acaagtgggg acacccctgc atatctgc ttcctctgc 2100  
tgttaagccc cagggagccc catccaccca gtggcctac agacaggcga atacacacac 2160  
accaagatag cttcagatc aacatgcac acactcaatg gtaatctt caaggttttc 2220  
ttttttttt cctgtttttt atttgttttgc tttttttttt ttttttgggtg 2280  
gtgggtggggc taccaaactt gaggcctaga gctaaaaatc atatagaaat gatgttatct 2340  
tgtgggtgtga ggaaaggcga gctggcctaa gttcacactt ttgtcccagt ggcctagac 2400  
tccaccacccagc cagctcccaa aatgaaaaaga ccacctgtca agcagcagtc aggagtctga 2460

tgtcacccat cactatttt tttccatcat tgtgcttgcc tctgcctcct tccacacccc 2520  
 tgtgacgtaa tcgcattggg aagccaggac aatgtttget gttctgtctt gggtaaaggg 2580  
 actccctgaa gctctgtggc tctccagtat ggtccctttt ctttcctaac agatgcata 2640  
 gttttcttca gaataacaata gtgattctta aaataaccca aaagacaggc atccacagt 2700  
 tgtgagcatg aatcacagcc tgcattgtgt gagtgtgaat agtgggataa aagtggatgt 2760  
 cagaagagtg gaaatcaaac ctctgcaaag caatcttct ctttctgtga agtgtattaa 2820  
 gaaatacctg aagtctgtgt gtgtgggtgt acccagactg tcaatcaata aagacccaga 2880  
 ctgtcaatga aaaaaaaaaaaaaaaa aaaaaaaaaaaaaaaa 2918

<210> 13  
<211> 3043  
<212> DNA  
<213> mouse

<400> 13  
 ctcagcgagg ggaaggggga ggaggcctgg atgactaaac ctgacagaaaa cgctgggtggg 60  
 aggctcgggc gggcgccagt gcccgcgtag gtccttctcg acccgccagcc accacccgccc 120  
 cggtgaccat gatagtgttt gtcaggttca actccagcta tggcttccca gtggaggtcg 180  
 attctgacac cagcatctt cagctcaagg aagtgggtgc taagcgacag ggggttccag 240  
 ctgaccagct gcgtgtgatt tttgccggga aggagcttcc gaatcacctg acggttcaaa 300  
 actgtgacct ggaacaacag agtattgtac acatagtaca gagaccacgg aggagaagtc 360  
 atgaaacaaa tgcacatggc ggggacgaac cccagagcac ctcagagggc tccatatggg 420  
 agtccaggag cttgacacga gtggacactga gcagccatac cctgcccgtg gactctgtgg 480  
 ggctggcggt cattctggac acagacagta agagggattc agaagcagcc agaggtccag 540  
 ttaaaccac ctacaacacg ttttcatct actgcaaagg cccctgccac aagggtccagc 600  
 ctggaaagct ccgagttcag tttggcacct gcaacaacgc aaccctcacc ttggccccagg 660  
 gcccacatctt ctggggacgtat gtcttaatcc caaaccggat gagtggtag tgccagtctc 720  
 cagactgccc tggaaaccaga gctgaatttt tctttaatcg tggagcacac ccaacctcag 780  
 acaaggacac gtcggtagct ttgaacactga tcaccagcaa caggcgccagc atcccttgca 840  
 tagcgtgcac agatgtcagg agccctgtcc tggcttccca gtgttaaccac cgtcacgtga 900  
 tctgttttgc ctgtttccac ttgtattgtg tcacaagact caacgatcg cagtttgc 960  
 acgatgtcact acctggctac tccctggcgt gtgtagttt ttttctggcgg ggactgttaag 1020  
 gaagcataacc atgaagggga ttgcgactca ctgcgtcaac cctcaggagc cacttctcag 1080  
 gcctacaggg tggacaaaag agccgctgag caagctcgct gggaggaggc ctccaaaggaa 1140  
 accatcaaga agaccaccaa gccttgcct cgcgtcaacg tgccaaatgt aaaaaacggaa 1200  
 ggatgtatgc acatgaagtg ttctcagccc cagtgcacgc tggagtgggt ctggaaactgt 1260  
 ggctgtgagt ggaaccgagc ctgcgtgggat gatcactggt ttgacgtgt aagagagatg 1320  
 tcacttggcc ctggacgcac aacctcaagg gaaactccga agatccctac cttccttagc 1380  
 catttcttct tctcgatgca tataagcaca taaatgcgcac cacacaaaca caggctgcag 1440  
 attacagaag cagccccatg atcctttctt gggcaccac agaaaaccac agcaccggct 1500  
 ggccccaggg ggaggaggca ctttcagccct ctggctcaact cgaatgtcag agettagatg 1560  
 aggggtgcacc tttggtttgg attctgttgc agccatgagt gaggtggaa gtgtttccca 1620  
 gggttgttgc caccgcctgg gtaagtaaca cctctgagga ttctcagaag cacacttgag 1680  
 atctgaggaa cgctgtctc atgttagtaat catctattcc caaaggcccc cctgcagtag 1740  
 tcaaaaactat ttgtttatcc ccccaaattcc tatcttaca aatggtgcgt atgagattac 1800  
 aacccctctg tgcactaattc agcttatcaa ccaagtgaga acctaggaaa gctaattgg 1860  
 tggcagactg cttaaatcgc agggaggact cagaagccaa acctacttcc gtctcgatgtca 1920  
 ttatctgcaatgc ctttagaaag aatgtatctt tttttcccccc tggaaaagata acaaagtctg 1980

caatttggtt tggagtattc ctactgcagc ctggaaagttt agcttcactg tgaatttaac 2040  
 agagaaaagtgc cctataaagg gggcggtttt aagagacaat cccatgatgc tgccccaatg 2100  
 ctaacaacag ggtcaagaaa cacaatgttt atagaaggag catccctcga ccacatcta 2160  
 gagagtatgc ctgaccctt ccaccacaag tggggacacc tctgcatac tgcctccctcc 2220  
 tctgctgtta agccccaggg agccccatcc acccagtggt cctacagaca gggcaataca 2280  
 cacacaccaa gatagccttc agatcaacat gcatcacact caagtgttaa tcttcaagg 2340  
 ttttcttttcc ttttctgt ttttatttg ttttgcctttt gcctttttt tttttttttt 2400  
 tgggtgggtggt ggggctacca aacttgaggc cttagagctaa aaatcatata gaaatgtatgt 2460  
 tatcttgtgg tgtgaggaaa ggccagctgg cctaaatgtca cactttgtc ccagtggccc 2520  
 tagactccac ccagccagct cccaaaatga aaagaccacc tgcataagcag cagtcaggag 2580  
 tctgatgtca cccatcacta tttttttcc atcattgtgc ttgcctctgc ctccctccac 2640  
 accccgtgtga cgtaatcgca ttgggaagcc aggacaatgtt tgcgtgttgc gcttgggtt 2700  
 aaggggactcc ctgaagctct gtggctctcc agtatgttcc cttttccctt ctaacagatg 2760  
 catatgtttt cttcagaata caatagtgtat tctaaaata accccaaaaga caggcatcca 2820  
 cagtggtgtga gcatgaatca cagcctgcatttgtgatgt tgaatagtgg gataaaaagtg 2880  
 gatgtcagaa gagtggaaat caaacacctt caaagcaatc tttctcttcc tgcgtgtgt 2940  
 attaagaaaat acctgaagtc tgcgtgtgt gttgttacca gactgtcaat caataaagac 3000  
 ccagactgtc aatgaaaaaaaaaaaaaaa aaaaaaaaaaaa aaa 3043

<210> 14  
 <211> 3253  
 <212> DNA  
 <213> mouse

<400> 14

ctcagcgagg ggaagggggaa ggaggcctgg atgactaaac ctgacagaaaa cgctgggtggg 60  
 aggctcgggc gggcgccagt gcccgcgtag gtccttctcg acccgccagcc accacccggcc 120  
 cgggtgaccat gatagtgtttt gtcagggttca actccagcta tggcttccca gtggagggtcg 180  
 attctgacac cagcatcttgcagctcaagg aagtgggtgc taagcgacgg ggttccagct 240  
 gaccagctgc gtgtgatttt tgccggaaag gagcttccga atcacctgac ggttcaaaac 300  
 tgtgacactgg aacaacagag tattgtacac atagtgacaga gaccacggag gagaagtcat 360  
 gaaacaaaatgc catctggagg ggacgaaacc cagacccatc cagagggtcc catatgggag 420  
 tccaggagct tgacacgagt ggacctgagc agccataaccc tgccgggtggc ctctgtgggg 480  
 ctggcggtca ttctggacac agacagtaag aggattcag aagcagccag aggtccagtt 540  
 aaacccacccatc acaacagctt ttccatctac tgccaaaggcc cctgccacaa ggttccagct 600  
 ggaaagctcc gagtcagtg tggcacctgc aaacaagcaa ccctcacctt ggcccaggcc 660  
 ccacatcttgc gggacgatgt cttaatttca aaccggatga gtggtgagtg ccagtctcca 720  
 gactgccctg gaaccagagc tgaatttttcc tttaaatgtg gaggcacaccc aacccatcagac 780  
 aaggacacgt cggtagctt gaacactgatc accagcaaca ggccgcagcat cccttgcata 840  
 gccgtgcacag atgtcaggag ccctgtctcg gtcttccaggt gtaaccaccc tcacgtgtac 900  
 tgggtggact gtttccactt gtattgtgtc acaagactca acgatggca gtttgcac 960  
 gatgctcaac ttggctactc cctgccgtgt gtagctggct gteccaaactc cctgattaaa 1020  
 gagctccatc acttcaggat ccttggagaa gagcagtgaca ctaggtacca gcagttatggg 1080  
 gcccggaaat gccgtgcacag aatggggaggt gtgtgtgc cccgtcctgg ctgtggagct 1140  
 ggactgtctac ctgaacaggg ccagagggaa gtccacctgcg aagggggcaa cggccctggc 1200  
 tgcgggttttgc ttttctgcgg ggactgttaag gaagcataacc atgaaggggaa ttgcactca 1260  
 ctgctcgaac cctcaggagc cacttctcag gcctacaggg tggacaaaag agccgctgag 1320  
 caagctcgct gggagggagcc ctccaaagaa accatcaaga agaccaccaa gccttgcct 1380

cgctgcaacg tgccaattga aaaaaacgga ggatgtatgc acatgaagtg tcctcagccc 1440  
 cagtgcacgc tggagtgggt ctggaaactgt ggctgtgagt ggaaccgagc ctgcataggg 1500  
 gatcaactggt ttgacgtgt a gagagagatg tcacttggcc ctggacgcac aacctaagg 1560  
 gaaactccga agattcttac cttcccttagc cattttttct ttcgtatgtcataaagcaca 1620  
 taaatgcgca cacacaaaca caggctgcag attacagaag cagccccctag atcccttcta 1680  
 gggcacccac agaaaaccac agcaccgcgt ggccccaggg ggaggaggca cttcagcct 1740  
 ctggctcaact cgaatgtcag agcttagatg aggggtgcacc tttggtttgg attctgtaga 1800  
 agccatgagt gaggtggaa gtgtttcca gggtttgtc cagccccctgg gtaagtaaca 1860  
 cctctgagga ttctcagaag cacactttagt atctgaggaa cgctgtctc atgttagaat 1920  
 catctattcc caaagggccc cctgcagtag tcaaaaactat ttgtttatcc ccccaaatcc 1980  
 tatcttaca aatggtgctg atgagattac aaccctctg tgtactaatac agcttatcaa 2040  
 ccaagtgaga accttaggaaa gctaattgga tggcagactg cttaaatcgc agggaggact 2100  
 cagaagccaa acctacttcc gttcgtttca ttatctgcaa cttagaaag aaatgatctt 2160  
 ttttcccccc tgaaaagata acaaagtctg caatttgggt tggagtttgc ctactgcagc 2220  
 ctggaaagttt agcttcactg tgaatttaac agagaaaagtgcctataaaagg gggcggtttt 2280  
 aagagacaat cccatgatgc tgcccaatg ctaacaacag ggtcaagaaa cacaatgttt 2340  
 atagaaggag caccctcga ccatctgaat gaggtatgc ctgaccctt ccaccacaag 2400  
 tggggacacc tctgcataatc tgctccctcc tctgtgtt a gccccaggg agccccatcc 2460  
 acccagtggt cctacagaca gggcaataca cacacacaa gatagccctc agatcaacat 2520  
 gcatcacact caagtgtttaa tctttcaagg ttttttttcc tttttctgtt tttttatcc 2580  
 ttttgctttt gctttttttt ttttttttgggtgggt ggggctacca aacttgaggc 2640  
 ctagagctaa aaatcatata gaaatgtatgt tatcttgtgg tgtgaggaaa gcccagctgg 2700  
 ctaagttca cactttgtc ccagtgccc tagactccac ccagccaggt cccaaaatga 2760  
 aaagaccacc tgtcaagcag cagtcaggag tctgtatgtca cccatcaacta tttttttcc 2820  
 atcattgtgc ttgcctctgc ctccctccac acccgtgtga cgtatcgca ttgggaagcc 2880  
 aggacaatgt ttgctgttct gctttgggtt aaggactcc ctgaagctct gtggctctcc 2940  
 agtatggtcc cttttcccttc ctaacagatg catatgtttt cttcagaata caatagtat 3000  
 tcttaaaaata accccaaaaga caggcatcca cagtcgtgtga gcatgaatca cagcctgcat 3060  
 tgtgtgagtg tgaatagtgg gataaaaagtgtatgttcaatggaaat acctgaagtc tttttttcc 3120  
 caaagcaatc tttcttttcc tttttttcc tttttttcc tttttttcc 3180  
 gtggtaccca gactgtcaat caataaagac ccagactgtc aatgaaaaaaaaaaaa 3240  
 aaaaaaaaaaaa aaa 3253

<210> 15  
 <211> 3254  
 <212> DNA  
 <213> mouse

<400> 15

ctcagcgagg ggaagggggg ggaggccctgg atgactaaac ctgacagaaa cgctgggg 60  
 aggctcgggc gggcgccagt gcccgcgtag gtccttctcg acccgcagcc accacccgccc 120  
 cggtgaccat gatagtgtttt gtcagggttca actccagcttca tggcttccca gtggagggtcg 180  
 attctgacac cagcatcttgcagtcaggaa aagtgggtgc taagcgacag ggggttccag 240  
 ctgaccagct gctgtgttattttccaggatgttcc gatcaccttca cggttcaaaa 300  
 ctgtgacccgttgcacaaacaga gtattgttaca catagtacag agaccacgga ggagaagtca 360  
 tgaaaacaaat gcatctggag gggacgaacc ccagagcacc tcagagggtcttccatatggg 420  
 gtccaggagc ttgacacgag tggacacttgcagccatacc ctggccgggtgg actctgtggg 480  
 gctggcggttc attctggaca cagacagtaa gaggttca gaagcagccaa gaggtccagt 540

taaacccacc tacaacagct ttttcatcta ctgcaaaggc ccctgccaca aggtccagcc 600  
tggaaagctc cgagtcagt gtggcacctg caaacaagca accctcacct tggcccaggg 660  
cccatcttgc tgggacgatg tcttaattcc aaaccggatg agtggtgagt gccagtcac 720  
agactgccct ggaaccagag ctgaatttt cttaaatgt ggagcacacc caacctcaga 780  
caaggacacg tcggtagctt tgaacctgat caccagcaac aggccgagca tcccttgcac 840  
agcgtgcaca gatgtcagga gcccgtctt ggttccag tgtaaccacc gtcacgtgat 900  
ctgtttggac tgtttccact tgtattgtgt cacaagactc aacgateggc agtttgtcca 960  
cgatgctcaa cttggctact ccctggcg ttagctggc tgcccactt ccctgattaa 1020  
agagtcacat cacttcagga tccttggaga agagcagtac actaggtacc agcagttatgg 1080  
ggccgaggaa tgcgtgctgc aatggggagg tgcgtgtgc ccccgtectg gctgtggc 1140  
tggactgcta cctgaacagg gccagaggaa agtcacctgc gaagggggca acggcctggg 1200  
ctgcggggtt gtttctgcc gggactgtaa ggaagcatac catgaagggg attgcgactc 1260  
actgctcgaa ccctcaggag cacttctca ggcctacagg gtggacaaa gagccgctga 1320  
gcaagctgc tgggaggagg cttcaagga aaccatcaag aagaccacca agccttgc 1380  
tcgctgcaac gtgccaattt aaaaaaaacgg aggatgtatg cacatgaagt gtcctcagcc 1440  
ccagtgcacag ctggagtgg tgcggactg tggctgtgag tggacccgag cctgcattggg 1500  
agatcaactgg ttgcgtgt agagagagat gtcacttgc cctggacgca caacctcaag 1560  
ggaaactccg aagatccca ctttccttag ccatttc ttcgtatgc atataagcac 1620  
ataaaatgcgc acacacaaac acaggctgca gattacagaa gcagccccata gatccttct 1680  
agggcaccctt cagaaacca cagcacccgc tggccccagg gggaggaggc acttcagcc 1740  
tctggctcac tcgaatgtca gagcttagat gagggtgcac ctttggttt gattctgttag 1800  
aagccatgag tgaggtgggaa agtggggcc aggggtgttgc ccacgccccgtt ggtaaatgtt 1860  
actctcgagg attctcgagaa gcacacttga gatctgagga acgctgctt catgtatgtt 1920  
tcatcttattt ccaaaggccc ccctgcagta gtcaaaacta tttgtttatc ccccaaaatc 1980  
ctatcttac aaatgggtct gatgagatta caacccctt gttactaat cagtttatca 2040  
accaagtggaa aacctaggaa agctaattgg atggcagact gcttaaatcg cagggaggac 2100  
tcagaagcca aacctacttc cgttcggtt attatctgca acttttagaaa gaaatgtatc 2160  
ttttttcccc ctgaaaagat aacaaagtct gcaatttgg tggagttt cctactgcag 2220  
cctggaaagt tagcttcaact gtgaattttaa cagagaaagt gcctataaaag gggcggtttt 2280  
taagagacaa tcccatgtat ctgcgccaat gctaacaaca gggtcaagaa acacaatgtt 2340  
tatagaagggaa gcatccctcg accatctgaa tgaggtatg cctgaccctt tccaccacaa 2400  
gtggggacac ctctgcataat ctgtccctc ctctgtgtt aagccccagg gagccccatc 2460  
caccctgg tccatcagac agggcaatac acacacacca agatgcctt cagatcaaca 2520  
tgcatacacac tcaagtgtt atctttcaag gttttttttt cttttccctg ttttttattt 2580  
gttttgcattt tgctttttttt tttttttttt ttgggtggg tggggctacc aaacttgagg 2640  
ccttagagcta aaaatccat agaaatgtat ttatcttgcgtt gttgtgggaa aggcagctg 2700  
gcctaagttc acactttgtt cccagtgccc ctagactcca cccagccagc tcccaaaatg 2760  
aaaagaccac ctgtcaagca gcaatcgatgat gtcgtatgtc acccatcaact atttttttc 2820  
catcattgtt cttgcctctg cttcccttca caccctgtt acgtatcgatc attggaaagc 2880  
caggacaatg tttgtgttc tgctttgggtt aaagggactc cctgaagctc tggctctc 2940  
cagtatggtc cttttccctt cttcccttca caccctgtt acgtatgtt gtcgtatgtc 3000  
ttcttaaaaat aacccaaaag acaggcatcc acagtgtgtg agcatgaatc acagcctgca 3060  
ttgtgtgagt gtgaatagtggataaaaagt ggatgtcaga agatggaaa tcaaacctct 3120  
gcaaaagcaat ctttctttt ctgtgaagtg tattaagaaa tacctgaagt ctgtgtgtt 3180  
ggtgttaccc agactgtcaa tcaataaaga cccagactgtt caatggaaaa aaaaaaaaaa 3240  
aaaaaaaaaaaa aaaa

3254

&lt;211&gt; 3253

&lt;212&gt; DNA

&lt;213&gt; mouse

&lt;400&gt; 16

ctcagcgagg ggaaggggga ggaggcctgg atgactaaac ctgacagaaaa cgctgggtggg 60  
aggctcgggc gggcgccagt gcccgcgtag gtccttctcg acccgcagcc accacccggcc 120  
cggtgaccat gatagtgttt gtcaggttca actccagcta tggcttccca gtggaggtcg 180  
attctgacac cagcatctg cagctcaagg aagtggttgc taagcgacag ggggttccag 240  
ctgaccagct gcgtgtgatt tttgccggga aggagcttcc gaatcacctg acggttcaaa 300  
actgtgacct ggaacaacag agtattgtac acatagtaca gagaccacgg gagaagtcat 360  
gaaacaaaatg catctggagg ggacgaaccc cagagcacct cagagggctc cataatgggag 420  
tccaggagct tgacacgagt ggacacctg agccatacccc tgccggtgga ctctgtgggg 480  
ctggcggtca ttctggacac agacagtaag agggatttag aagcagccag aggtccagtt 540  
aaacccacct acaacagctt tttcatctac tgcaaaaggcc cctgccacaa ggtccagcct 600  
gaaagctcc gagttcagtg tggcacctgc aaacaagcaa ccctcacctt ggcccagggc 660  
ccatcttgct gggacgatgt cttattcca aacggatga gtggtgagtg ccagtctcca 720  
gactgcccgt gaaccagagc tgaatttttc tttaaatgtg gagcacaccc aacctcagac 780  
aaggacacgt cggtagctt gaacctgate accagcaaca ggccgagcat cccttgcat 840  
gcgtgcacag atgtcaggag ccctgtccgt gtcttcagt gtaaccacgg tcacgtgatc 900  
tgtttggact gtttccactt gtattgtgtc acaagactca acgatcggtca gtttggccac 960  
gatgctcaac ttggctactc cctggctgt gttagtggct gtcccaactc cctgattaaa 1020  
gagctccatc acttcaggat cttggagaa gagcagtaca ctaggtacca gcagtatggg 1080  
gccgaggaat gcgtgtgc aatgggaggt gtgctgtgcc cccgtcctgg ctgtggagct 1140  
ggactgtctac ctgaacaggg ccagagggaa gtcacctgcg aagggggcaa cggcctgggc 1200  
tgcgggtttg tttctggcg ggactgttaag gaagcatacc atgaagggga ttggactca 1260  
ctgctcgaac cctcaggagc cacttctca gcttacaggg tggacaaaag agccgctgag 1320  
caagctcgct gggaggagc ctccaaggaa accatcaaga agaccaccaa gccttgcct 1380  
cgctgcaacg tgccaattga aaaaaacgga ggatgtatgc acatgaagtgc tccctcagccc 1440  
cagtgcacgc tggagtgggt ctggaaactgt ggctgtgagt ggaaccgagc ctgcattggg 1500  
gatcaactggt ttgacgtgtt gagaagatg tcacttggcc ctggacgcac aacctcaagg 1560  
gaaactccga agatcttac cttccttagc catttcttct tctcgatgca tataaggcaca 1620  
taaatgcgca cacacaaaca caggctgcag attacagaag cagccccatc atcccttcta 1680  
gggcacccac agaaaaccac agcacccctgt ggccccaggg ggaggaggca ctccctgact 1740  
ctggctcaact cgaatgtca gacttagatg agggtgcacc tttggttttgg attctgtaga 1800  
agccatgagt gaggtggaa gtgtttccca ggggtgttgc cacgcctgg gtaagtaaca 1860  
cctctgagga ttctcagaag cacacttgcg atctgaggaa cgctgtctc atgttagata 1920  
catctattcc caaaggcccc cctgcagtag tcaaaactat ttgtttatcc ccccaaattcc 1980  
tatctttaca aatggtgcg atgagattac aaccctctg tttactataatc agcttatcaa 2040  
ccaagtgaga accttagaaaa gctaatttggaa tggcagactg cttaaatcgc agggaggact 2100  
cagaagccaa acctacttcc gttcggttca ttatctgcaaa cttagaaaa agatgtatctt 2160  
ttttcccccc taaaaagata acaaagtctg caatttgggtt tggagtttcc ctactgcagc 2220  
ctggaaagttt agcttcactg tgaatttaac agagaaaatg cctataaaagg gggcggtttt 2280  
aagagacaat cccatgtgc tgcgcacatg ctaacaacag ggtcaagaaaa cacaatgttt 2340  
atagaaggag catccctcga ccatctgaat gagagtatgc ctgacccctt ccaccacaaag 2400  
tggggacacc tctgcataatc tgcctccctcc tctgtgtta agccccaggg agcccccattcc 2460  
acccagtggc cttacagaca gggcaataca cacacaccaa gatagccttc agatcaacat 2520  
gcatcacact caagtgttaa tcttcaagg ttttcttcc tttttcctgt tttttatgg 2580

ttttgctttt gctttttttt tttttttttt tggtgggtggt ggggctacca aacttgaggc 2640  
 ctagagctaa aaatcatata gaaatgatgt tatcttgtgg tgtgaggaaaa ggccagctgg 2700  
 cctaagttca cactttgtc ccagtggccc tagactccac ccagccagct cccaaaatga 2760  
 aaagaccacc tgteaagcag cagtcaggag tctgatgtca cccatacta tttttttcc 2820  
 atcattgtgc ttgcctctgc ctccctccac acccggtgtga cgtaatcgca ttgggaagcc 2880  
 aggacaatgt ttgcgttct gctttggta aaggactcc ctgaagctct gtggctctcc 2940  
 agtatggtcc ctttcccttc ctaacagatg cataatgtttt ctgcagaata caatagtgtat 3000  
 tcttaaaaata accccaaaaga caggcatcca cagtggtgtga gcatgaatca cagcctgcat 3060  
 tgtgtgaggta tgaatagtgg gataaaaagtg gatgtcagaa gagtgaaat caaacctctg 3120  
 caaagcaatc ttctctttc tgtgaagtgt attaagaaat acctgaagtc tgtgtgtgtg 3180  
 gtggtaccca gactgtcaat caataaagac ccagactgtc aatgaaaaaaaaaaaa 3240  
 aaaaaaaaaaaa aaa 3253

<210> 17  
 <211> 3092  
 <212> DNA  
 <213> mouse

<400> 17

ctcagcgagg ggaaggggga ggaggcctgg atgactaaac ctgacagaaaa cgctgggtgg 60  
 aggctcgggc gggcgccagt gcccgcgtag gtccttctcg acccgccagcc accacccgcc 120  
 cggtgaccat gatagtaact gtgacctgga acaacagagt attgtacaca tagtacagag 180  
 accacggagg agaagtcatg aaacaaaatgc atctggaggg gacgaacccc agagcaccc 240  
 agagggctcc atatgggagt ccaggagctt gacacgagtg gacctgagca gcccataccct 300  
 gccgggtggac tctgtggggc tggcggtcat tctggacaca gacagtaaga gggattcaga 360  
 agcagccaga ggtccagtt aacccaccta caacagcttt ttcatctact gcaaaggccc 420  
 ctgccacaag gtccagcctg gaaagctccg agttcagtgt ggcacctgca aacaagcaac 480  
 cctcaccttgc gcccaggggcc catcttgcgtg ggacgatgtc ttaattccaa accggatgag 540  
 tggtgagtgc cagtcctccag actgccttgg aaccagagct gaatttttct ttaaatgtgg 600  
 agcacaccca acctcagaca aggacacgtc ggtagctttt aacctgatca ccagcaacag 660  
 ggcgcagcattc cttgcatacg cgtgcacaga tgtcaggagc cctgtccctgg tcttccagtg 720  
 taaccacccgt cacgtatctt gtttggactg tttccacttg tattgtgtca caagactcaa 780  
 cgatcgccag tttgtccacg atgctcaact tggctactcc ctggcggtgt tagctggctg 840  
 tcccaactcc ctgattaaag agctccatca ctgcaggatc cttggagaag agcactacac 900  
 taggtaccag cagtagtgggg ccgaggaatg cgtgctgcaa atgggaggtg tgctgtgccc 960  
 ccgtccctggc tgtggagctg gactgctacc tgaacagggc cagagggaa tcacctgcga 1020  
 agggggcaac ggcctggct gccccgggtt tttctgcggg gactgttaagg aagcataccca 1080  
 tgaaggggat tgcgactcac tgctcgaacc ctcaggagcc acttctcagg cctacagggt 1140  
 ggacaaaaga gcccgtgac aagctegctg ggaggaggcc tccaaaggaaaa ccatcaagaa 1200  
 gaccaccaag cttgtccctc gctgcaacgt gccaattgaa aaaaacggag gatgtatgca 1260  
 catgaagtgt cctcagcccc agtgcaagct ggagtgggtgc tggaaactgtg gctgtgagtg 1320  
 gaaccggagcc tgcatggag atcactgggt tgacgtgttag agagagatgt cacttggccc 1380  
 tggacgcaca acctcaaggg aaactccgaa gattcctacc ttcccttagcc atttcttctt 1440  
 ctcgatgcat ataagcacat aaatgcgcac acacaacac aggctgcaga ttacagaagc 1500  
 agccccctaga tccttcttag ggcacccaca gaaaaccaca gcacccgctg gccccagggg 1560  
 gaggaggccac ttctcagcctc tggctcactc gaatgtcaga gcttagatga ggggtgcaccc 1620  
 ttgggtttggaa ttctgttagaa gccatgagtg aggtgggaag tgttttccag ggttggcc 1680  
 acggccctggg taagtaacac ctctgaggat tctcagaagc acacttggagaac 1740

gctgctctca tgttagtaatc atctattccc aaagggcccc ctgcagtagt caaaaactatt 1800  
 tggtttatccc cccaaatccct atctttacaa atggtgtctga tgagattaca acccctctgt 1860  
 gtactaatca gcttatcaac caagtgagaa cctaggaaag ctaattggat ggcagactgc 1920  
 ttaaatcgca gggaggactc agaagccaaa cctacttccg ttcgtttcat tatctgcaac 1980  
 ttttagaaaga aatgatcttt ttttccctt gaaaagataa caaagtctgc aatttggttt 2040  
 ggagtattcc tactgcagcc tggaaagttt gcttcactgt gaatttaaca gagaaaagtgc 2100  
 ctataaaggg ggcgtttta agagacaatc ccatgatgtc gcgcctatgc taacaacagg 2160  
 gtcaagaaac acaatgtttt tagaaggagc atccctcgac catctgaatg agagtatgcc 2220  
 tgacccttc caccacaagt ggggacacct ctgcataatct gctccctctt ctgctgttaa 2280  
 gccccaggga gccccatcca cccagtggcctt ctacagacag ggcaatacac acacaccaag 2340  
 atagccttca gatcaacatg catcacactc aagtgttaat ctttcaaggt tttctttctt 2400  
 ttttcctgtt ttttattttgt tttgctttt ctttttttt tttttttttt ggtgggtgg 2460  
 gggctaccaa acttggggcc tagagctaaa aatcatatag aaatgatgtt atettgtgg 2520  
 gtgagggaaag gccagctggc ctaagttcac acttttgcc cagtggccctt agactccacc 2580  
 cagccagctc cccaaatgaa aagaccaccc gtcaaggcage agtcaggagt ctgatgtcac 2640  
 ccatcaactat ttttttcca tcattgtgtc tgcctctgccc tccctccaca cccgtgtgac 2700  
 gtaatcgcat tggaaagccca ggacaatgtt tgctgttctg ctggggtaa agggactccc 2760  
 tgaagctctg tggctctcca gtatggtccc ttttcttcc taacagatgc atatgtttc 2820  
 ttcagaatac aatagtgtt cttaaaataa cccaaaagac aggcatccac agtgtgtgag 2880  
 catgaatcac agcctgcatt gtgtgagtgt gaatagtggg ataaaagtg atgtcagaag 2940  
 agtggaaatc aaacctctgc aaagcaatct ttctctttctt gtgaagtgtta ttaagaaata 3000  
 cctgaagtct gtgtgtgtgg tggtaaccag actgtcaatc aataaagacc cagactgtca 3060  
 atgaaaaaaaaaaaaaaa aaaaaaaaaaa aa 3092

<210> 18  
 <211> 3255  
 <212> DNA  
 <213> mouse

<400> 18

ctcagcgagg ggaaggggggaa ggaggcctgg atgactaaac ctgacagaaaa cgctgggtggg 60  
 aggctcgggc gggcgccagt gcccgcgtag gtccttctcg acccgccagcc accacccgccc 120  
 cggtagccat gatagtgttt gtcaggttca actccagcta tggcttccca gtggaggtcg 180  
 attctgacac cagcatcttgcagtcagg aagtgggtgc taagcgacag ggggttccag 240  
 ctgaccagct gcgtgtgatt tttggccgggaa aggagcttcc gaatcacccgt acgggttcaaa 300  
 actgtgactt ggaacaacag agtattgtac acatagtaca gagaccacgg aggagaagtc 360  
 atgaaacaaa tgcacatcgaa ggggacgaac cccagagcac ctcagagggc tccatatggg 420  
 agtccaggag cttgacacga gtggacctga gcagccatac cctgcccgggt gactctgtgg 480  
 ggctggcggt cattctggac acagacagta agagggattc agaagcagcc agaggtccag 540  
 ttaaacccac ctacaacacgc ttttcatct actgcaaaagg cccctgcccac aagggtccage 600  
 ctggaaatct ccgagttcag tggacccactt gcaaaacaagg aaccctcacc ttggcccagg 660  
 gccccatcttgc tgggacgtatc tttttttttt gggggggat ggggggtgag tgccagttc 720  
 cagactgccc tggaaaccaga gctgaatttt tttttttttt tggggggat gggggggat ggggggtgag tgccagttc 780  
 acaaggacac gtcgttagct tggaaacctga tcaccagcaaa cggcgccagc atcccttgc 840  
 tagcgtgcac agatgtcagg agccctgtcc tgggtttccaa gtgttaaccac cgtcacgtga 900  
 tctgttttggaa ctgtttccac ttgttattgttgc tcacaagact caacgatcgg cagtttgc 960  
 acgatgtctca acttggctac tccctggcgt gtgtagctgg ctgtccaaac tccctgatta 1020  
 aagagctcca tcacttcagg atccttggag aagagcagta cactaggtac cagcagttatg 1080

3255

<210> 19  
<211> 3255  
<212> DNA  
<213> mouse

<400> 19

ctcagcgagg ggaagggggga ggaggcctgg atgactaaac ctgacagaaa cgctggtggg 60  
aggctcgggc gggcgccagt gccccgttag gtcccttcctcg acccgcagcc accaccggcc 120  
cggtgaccat gatagtgttt gtcaggttca actccagctta tggcttccca gtggaggtcg 180  
attctgacac cagcatcttg cagctcaagg aagtgggtgc taagcgacag ggggttccag 240

tcgtaccatggc ctttgcgggaa aggagacctcc gaatcacctg acgggttcaaa 300  
actgtgaccc ggaacaacag agtattgtac acatagtaca gagaccacgg aggagaagtc 360  
atgaaacaaa tgcatacttggc ggggacaaac cccagagcac ctcagaggc tecatatggg 420  
agtccaggag cttgacacga gtggacactga gcagccatac cctgcgggtg gactctgtgg 480  
ggctggcggt cattctggac acagacagta agagggatc agaagcagcc agagggtccag 540  
ttaaaccac ctacaacagc ttttcatct actgcaaagg cccctgccac aaggtccagc 600  
ctggaaagct ccgagttcag ttttgcaccc gcaaacaagg aaccctcacc ttggcccagg 660  
gccccatcttgc tggggacgtat gtcttaatcc caaacccggat gagttgttag tgccagtctc 720  
cagactgccc tggaaaccaga gctgaatttt tctttaaatg tggagcacac ccaacccctcag 780  
acaaggacac gtccggtagct ttgaacctga tcaccagcaa caggcgcagc atcccttgca 840  
tagcgtgcac agatgtcagg agccctgtcc tggcttccca gtgtaaaccac cgtcacgtga 900  
tctgtttggc ctgtttccac ttgtattgtc tcacaagact caacgategg cagtttgc 960  
acgatgtca acttggctac tccctggcgt gttagctgg ctgtcccaac tccctgatta 1020  
aagagctcca tcacttcagg atccttggag aagagcagta cactaggtac cagcagtatg 1080  
ggggccgagga atgcgtgtg caaatggggat gtgtgtgtg cccccgttgc ggctgtggag 1140  
ctggactgtt acctgaacag gcccagagga aagtccatcg cgaagggggc aacggccctgg 1200  
gctgcgggtt tggggactgtc cgggactgtc aggaagcata ccatgaaggg gattgtggact 1260  
cactgctcga accctcagga gccacttctc aggcctacag ggtggacaaa agagccgtc 1320  
agcaagctcg ctggggaggag gcttccaaagg aaaccatcaa gaagaccaac aagccttgc 1380  
ctcgctgcaaa cgtccaaatt gaaaaaaaaacg gaggatgtat gcacatgaag tgccttcagc 1440  
cccagtgcac gctggagtgg tgctggaaact gtggctgtc gtggaaaccgc gcctgcattgg 1500  
gagatcaactg gtttgcacgtc tagagagaga tgcacttgg ccctggacgc acaacccatca 1560  
ggggaaactcc gaagatccatcc accttccatc gccatttctt cttctcgatg catataagca 1620  
cataaaatgcg cacacacaaa cacaggctgc agattacaga agcagccccct agatcccttc 1680  
tagggcaccac acagaaaaacc acagcaccccg ctggccccag ggggaggagg cactttcagc 1740  
ctctggctca ctcgaatgtc agagcttgc tgagggtca cctttgggtt ggattctgt 1800  
gaagccatga gtgagggtggg aagtgttttc cagggttgtt gccacgcctt gggtaagtaa 1860  
cacctctgag gattctcaga agcacaactt agatctgagg aacgctgtc tcatgttagta 1920  
atcatctatt cccaaaggcc cccctgcagt agtcaaaaact atttgggtt ccccccataat 1980  
cctatcttca caaatgggtc tgatgagatt acaacccctt tgcacttgc tcaagtttac 2040  
aaccacgtca gaaccttagga aagctaattt gatggcagac tgcattaaatc gcagggagga 2100  
ctcagaagcc aaacctactt ccgttcgttt cattatctgc aacttttagaa agaaatgatc 2160  
ttttttccctt cctgaaaaga taacaaatgc tgcaattttgg tttggaggat tgcacttgc 2220  
gcctggaaatgt ttagtttcac tgcattttta acagagaaaat tgcctataaaa gggggcggtt 2280  
ttaagagaca atccccatgt gtcgcacca tgcataacaac agggtaaga aacacaatgt 2340  
ttatagaagg agcatccctc gaccatctgc atgagagat tgcctgaccc ttccaccac 2400  
agtggggaca cctctgcata tctgccttccct cctctgtgt taagccccag ggagccccat 2460  
ccacccactg gtcctacaga cagggcaata cacacacacc aagatagcc tcaatgtcaac 2520  
atgcattcaca ctcataatgtt aatcttcaaa ggttttctt tcttttctt gttttttatt 2580  
tgcattttttt tgcattttttt tttttttttt tttttttttt tttttttttt tttttttttt 2640  
gccttagagct aaaaatcata tagaaatgtt gttatctgtt ggtgtgagga aaggccagct 2700  
ggcctaagtt cacacttttgc tccctgtggc cctagactcc accccagccag ctcccaaat 2760  
gaaaagacca cctgtcaagc agcagtcagg agtctgtatgtt caccatcac tattttttttt 2820  
ccatcattgt gcttccttcgc tgcattttccca acacccgtgt gacgtatcg cattggggaaag 2880  
ccaggacaat gtttgcgtt ctgcattttggg taaagggact ccctgaagct ctgtggctc 2940  
ccagttatgtt ccctttccct tgcataacaga tgcataatgtt ttcttcagaa tacaatagt 3000  
attcttaaaa taacccaaaaa gacaggcata cacagtgtgtt gagcatgaat cacacccgtc 3060  
attgtgttagt tgcataatgtt gggataaaaag tggatgtcag aagagtggaa atcaaaaccc 3120

tgcaaagcaa tctttcttctt tctgtgaagt gtattaagaa atacctgaag tctgtgtgtg 3180  
 tggtgttacc cagactgtca atcaataaaag acccagactg tcaatgaaaa aaaaaaaaaa 3240  
 aaaaaaaaaa aaaaaa 3255

<210> 20  
 <211> 3255  
 <212> DNA  
 <213> mouse

&lt;400&gt; 20

ctcagcgagg ggaaggggga ggaggcctgg atgactaaac ctgacagaaa cgctgggtggg 60  
 aggctcgccc gggcccaagt gccccgttag gtccttctcg accecgagcc accacccggcc 120  
 cggtgaccat gatagtgttt gtcaggttca actccagcta tggcttccca gtggaggtcg 180  
 attctgacac cagcatctt cagctcaagg aagtgggtgc taagcgacag ggggttccag 240  
 ctgaccagct gcgtgtgatt tttggggga aggagcttcc gaatcacctg acgggttcaaa 300  
 actgtgacact ggaacaacag agtattgtac acatagtaca gagaccacgg aggagaagtc 360  
 atgaaaacaaa tgcacatctt ggggacgaaac cccagagcac ctcagaggc tccatatggg 420  
 agtccaggag cttgacacga gtggacactga gcagccatac cttgcgggtg gactctgtgg 480  
 ggctggcggt cattctggac acagacagta agagggattc agaagcgaccc agaggtccag 540  
 ttaaacccac ctacaacagc ttttcatct actgcaaagg cccctgccac aagggtccagc 600  
 ctggaaagct ccgagttcag tgtggcacct gcaaacaaggc aaccctcacc ttggcccagg 660  
 gccccatctt ctgggacgat gtcttaattt caaaccggat gagtggtgag tgccagtetc 720  
 cagactgccc tggaaaccaga gctgaatttt tctttaatg tggagcacac ccaacctcag 780  
 acaaggacac gtcggtagct ttgaacctga tcaccagcaa caggcgacgc atcccttgca 840  
 tagcgtgcac agatgtcagg agccctgtcc tggcttccca gtgttaaccac cgtcacgtga 900  
 tctgttttga ctgtttccac ttgtattgtg tcacaagact caacgatcgg cagttgtcc 960  
 acgatgtca acttggctac tccctggcggt gtgttagctgg ctgtcccaac tccctgatta 1020  
 aagagctcca tcacttcagg atccctggag aagagcagta cactaggtac cagcagtatg 1080  
 gggccgagga atgcgtgctg caaatgggag gtgtgctgtg ccccccgtct ggctgtggag 1140  
 ctggactgct acctgaacag ggccagagga aagtccacctg cgaagggggc aacggcctgg 1200  
 gctgcgggtt tgtttctgc cgggactgtt aggaagcata ccatgaaggg gattgcgact 1260  
 cactgctcga accctcagga gccacttctc aggcctacag ggtggacaaa agagccgctg 1320  
 agcaagctcg ctgggaggag gcctccaagg aaaccatcaa gaagaccacc aagccttgtc 1380  
 ctcgctgcatt cgtcccaatt gaaaaaaaaacg gaggatgtat gcacatgaag tgccttcagg 1440  
 cccagtgcatt gctggagtgg tgcttggact gtggctgtga gttagaaccga gcctgcattgg 1500  
 gagatcactg gtttgcgtg tagagagaga tgcacttgg ccctggacgc acaacctcaa 1560  
 gggaaactcc gaagattcct accttccttta gccatttctt cttctcgatg catataagca 1620  
 cataaatgcg cacacacaaa cacaggctgc agattacaga aecagccccct agatcccttc 1680  
 tagggcaccc acagaaaacc acagcaccccg ctggccccag ggggaggagg cacttcagg 1740  
 ctctggctca ctcgaatgtc agagcttaga tgagggtgca cttttgggtt ggattctgtt 1800  
 gaagccatga gtgagggtggg aagtgtttt caggggtgtt gccacccctt gggtaagtaa 1860  
 cacctcttagt gattctcaga agcacacttg agatctgagg aacgctgttc tcatgttagta 1920  
 atcatctatt cccaaagggc cccctgcagt agtcaaaaact atttgggtt ccccccaat 1980  
 cctatcttta caaatggtgc tgatgagatt acaacccctc tgcgtactaa tcagcttate 2040  
 aaccaagtga gaaccttagga aagctaattt gatggcagac tgctttaatc gcaggggagga 2100  
 ctcagaagcc aaacctactt ccgttcgttt cattatctgc aacttttagaa agaaatgate 2160  
 ttttttccctt cctgaaaaga taacaaagtc tgcaatttgg tttggagttat tcctactgca 2220  
 gctggaagt ttagcttac tgcgttgcattt aacagagaaaac gggggcgttt 2280

ttaagagaca atccatgat gctgcgccaa tgctaacaac agggtcaaga aacacaatgt 2340  
ttatagaagg agcatccctc gaccatctga atgagagtat gcctgacccc ttccaccaca 2400  
agtggggaca cctctgcata tctgctccct cctctgctgt taagccccag ggagccccat 2460  
ccacccagtg gtcctacaga cagggcaata cacacacacc aagatagcct tcagatcaac 2520  
atgcattcaca ctcaagtgtt aatcttcaa gttttcttt tcttttcct gtttttatt 2580  
tgttttgctt ttgctttttt tttttttt tttgggtgt gtggggctac caaacttgag 2640  
gccttagagct aaaaatcata tagaaatgat gttatcttgc ggtgtgagga aaggccagct 2700  
ggcctaagtt cacacttttgc tcccagtggc cctagactcc acccagccag ctcccaaat 2760  
gaaaagacca cctgtcaagc agcagtcagg agtctgatgt caccctateac tattttttt 2820  
ccatcattgt gcttgcctct gcctccttcc acacccgtgt gacgtaatcg cattggaaag 2880  
ccaggacaat gtttgcgtt ctgctttggg taaagggact ccctgaagct ctgtggctct 2940  
ccagtatggc ccctttcct tcctaacaga tgcataatgtt ttcttcagaa tacaatagtg 3000  
attcttaaaa taacccaaaaa gacaggcatc cacagtgtgt gagcatgaat cacagcctgc 3060  
attgtgtgag tgtgaatagt gggataaaag tggatgtcag aagagtggaa atcaaaccctc 3120  
tgcaaagcaa tctttcttt tctgtgaagt gtattaagaa atacctgaag tctgtgtgt 3180  
tggtggtacc cagactgtca atcaataaag acccagactg tcaatgaaaa aaaaaaaaaa 3240  
aaaaaaaaaa aaaaaa 3255

&lt;210&gt; 21

&lt;211&gt; 105

&lt;212&gt; PRT

&lt;213&gt; mouse

&lt;400&gt; 21

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Ile | Val | Phe | Val | Arg | Phe | Asn | Ser | Ser | Tyr | Gly | Phe | Pro | Val | Glu |
| 1   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Asp | Ser | Asp | Thr | Ser | Ile | Leu | Gln | Leu | Lys | Glu | Val | Val | Ala | Lys |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Gln | Gly | Val | Pro | Ala | Asp | Gln | Leu | Arg | Val | Ile | Phe | Ala | Gly | Lys |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Leu | Pro | Asn | His | Leu | Thr | Val | Gln | Leu | Asn | Pro | Pro | Thr | Thr | Ala |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Ser | Ser | Thr | Ala | Lys | Ala | Pro | Ala | Thr | Arg | Ser | Ser | Leu | Glu | Ser |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Glu | Phe | Ser | Val | Ala | Pro | Ala | Asn | Lys | Gln | Pro | Ser | Pro | Trp | Pro |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

|     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Ala | His | Leu | Ala | Gly | Thr | Met | Ser |
|     |     |     |     |     |     |     |     |     |
|     |     |     |     |     |     |     |     |     |
|     |     |     |     |     |     |     |     |     |

&lt;210&gt; 22

<211> 344  
<212> PRT  
<213> mouse

&lt;400&gt; 22

Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
1 5 10 15

Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
20 25 30

Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
35 40 45

Glu Leu Pro Asn His Leu Thr Val Gln Gly Pro Ser Cys Trp Asp Asp  
50 55 60

Val Leu Ile Pro Asn Arg Met Ser Gly Glu Cys Gln Ser Pro Asp Cys  
65 70 75 80

Pro Gly Thr Arg Ala Glu Phe Phe Lys Cys Gly Ala His Pro Thr  
85 90 95

Ser Asp Lys Asp Thr Ser Val Ala Leu Asn Leu Ile Thr Ser Asn Arg  
100 105 110

Arg Ser Ile Pro Cys Ile Ala Cys Thr Asp Val Arg Ser Pro Val Leu  
115 120 125

Val Phe Gln Cys Asn His Arg His Val Ile Cys Leu Asp Cys Phe His  
130 135 140

Leu Tyr Cys Val Thr Arg Leu Asn Asp Arg Gln Phe Val His Asp Ala  
145 150 155 160

Gln Leu Gly Tyr Ser Leu Pro Cys Val Ala Gly Cys Pro Asn Ser Leu  
165 170 175

Ile Lys Glu Leu His His Phe Arg Ile Leu Gly Glu Glu Gln Tyr Thr  
180 185 190

Arg Tyr Gln Gln Tyr Gly Ala Glu Glu Cys Val Leu Gln Met Gly Gly  
195 200 205

Val Leu Cys Pro Arg Pro Gly Cys Gly Ala Gly Leu Leu Pro Glu Gln  
210 215 220

Gly Gln Arg Lys Val Thr Cys Glu Gly Gly Asn Gly Leu Gly Cys Gly

225                   230                   235                   240

Phe Val Phe Cys Arg Asp Cys Lys Glu Ala Tyr His Glu Gly Asp Cys  
245                   250                   255

Asp Ser Leu Leu Glu Pro Ser Gly Ala Thr Ser Gln Ala Tyr Arg Val  
260                   265                   270

Asp Lys Arg Ala Ala Glu Gln Ala Arg Trp Glu Glu Ala Ser Lys Glu  
275                   280                   285

Thr Ile Lys Lys Thr Thr Lys Pro Cys Pro Arg Cys Asn Val Pro Ile  
290                   295                   300

Glu Lys Asn Gly Gly Cys Met His Met Lys Cys Pro Gln Pro Gln Cys  
305                   310                   315                   320

Lys Leu Glu Trp Cys Trp Asn Cys Gly Cys Glu Trp Asn Arg Ala Cys  
325                   330                   335

Met Gly Asp His Trp Phe Asp Val  
340

<210> 23

<211> 63

<212> PRT

<213> mouse

<400> 23

Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
1                   5                   10                   15

Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
20                   25                   30

Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
35                   40                   45

Glu Leu Pro Asn His Leu Thr Val Gln Leu Ala Val Pro Thr Pro  
50                   55                   60

<210> 24

<211> 153

<212> PRT

<213> mouse

&lt;400&gt; 24

Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
1 5 10 15

Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
20 25 30

Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
35 40 45

Glu Leu Pro Asn His Leu Thr Val Gln Asn Cys Asp Leu Glu Gln Gln  
50 55 60

Ser Ile Val His Ile Val Gln Arg Pro Arg Arg Arg Ser His Glu Thr  
65 70 75 80

Asn Ala Ser Gly Gly Asp Glu Pro Gln Ser Thr Ser Glu Gly Ser Ile  
85 90 95

Trp Glu Ser Arg Ser Leu Thr Arg Val Asp Leu Ser Ser His Thr Leu  
100 105 110

Pro Val Asp Ser Val Gly Leu Ala Val Ile Leu Asp Thr Asp Ser Lys  
115 120 125

Arg Asp Ser Glu Ala Ala Arg Gly Pro Gly Pro Ile Leu Leu Gly Arg  
130 135 140

Cys Leu Asn Ser Lys Pro Asp Glu Trp  
145 150

&lt;210&gt; 25

&lt;211&gt; 194

&lt;212&gt; PRT

&lt;213&gt; mouse

&lt;400&gt; 25

Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
1 5 10 15

Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
20 25 30

Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
35 40 45

Glu Leu Pro Asn His Leu Thr Val Gln Asn Cys Asp Leu Glu Gln Gln

|    |    |    |
|----|----|----|
| 50 | 55 | 60 |
|----|----|----|

Ser Ile Val His Ile Val Gln Arg Pro Arg Arg Arg Ser His Glu Thr  
 65                    70                    75                    80

Asn Ala Ser Gly Gly Asp Glu Pro Gln Ser Thr Ser Glu Gly Ser Ile  
 85                    90                    95

Trp Glu Ser Arg Ser Leu Thr Arg Val Asp Leu Ser Ser His Thr Leu  
 100                  105                  110

Pro Val Asp Ser Val Gly Leu Ala Val Ile Leu Asp Thr Asp Ser Lys  
 115                  120                  125

Arg Asp Ser Glu Ala Ala Arg Gly Pro Val Lys Pro Thr Tyr Asn Ser  
 130                  135                  140

Phe Phe Ile Tyr Cys Lys Gly Pro Cys His Lys Val Gln Pro Gly Lys  
 145                  150                  155                  160

Leu Arg Val Gln Cys Gly Thr Cys Lys Gln Ala Thr Leu Thr Leu Ala  
 165                  170                  175

Gln Asn Phe Ser Leu Asn Val Glu His Thr Gln Pro Gln Thr Arg Thr  
 180                  185                  190

**Arg Arg**

<210> 26  
<211> 183  
<212> PRT  
<213> mouse

<400> 26  
Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
 1                    5                    10                    15

Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
 20                  25                  30

Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
 35                  40                  45

Glu Leu Pro Asn His Leu Thr Val Gln Asn Cys Asp Leu Glu Gln Gln  
 50                  55                  60

Ser Ile Val His Ile Val Gln Arg Pro Arg Arg Arg Ser His Glu Thr  
65 70 75 80

Asn Ala Ser Gly Gly Asp Glu Pro Gln Ser Thr Ser Glu Gly Ser Ile  
85 90 95

Trp Glu Ser Arg Ser Leu Thr Arg Val Asp Leu Ser Ser His Thr Leu  
100 105 110

Pro Val Asp Ser Val Gly Leu Ala Val Ile Leu Asp Thr Asp Ser Lys  
115 120 125

Arg Asp Ser Glu Ala Ala Arg Gly Pro Val Lys Pro Thr Tyr Asn Ser  
130 135 140

Phe Phe Ile Tyr Cys Lys Gly Pro Cys His Lys Val Gln Pro Gly Lys  
145 150 155 160

Leu Arg Val Gln Cys Gly Thr Cys Lys Gln Ala Thr Leu Thr Leu Ala  
165 170 175

Gln Leu Ala Val Pro Thr Pro  
180

<210> 27

<211> 296

<212> PRT

<213> mouse

<400> 27

Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
1 5 10 15

Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
20 25 30

Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
35 40 45

Glu Leu Pro Asn His Leu Thr Val Gln Asn Cys Asp Leu Glu Gln Gln  
50 55 60

Ser Ile Val His Ile Val Gln Arg Pro Arg Arg Arg Ser His Glu Thr  
65 70 75 80

Asn Ala Ser Gly Gly Asp Glu Pro Gln Ser Thr Ser Glu Gly Ser Ile  
85 90 95

Trp Glu Ser Arg Ser Leu Thr Arg Val Asp Leu Ser Ser His Thr Leu  
100 105 110

Pro Val Asp Ser Val Gly Leu Ala Val Ile Leu Asp Thr Asp Ser Lys  
115 120 125

Arg Asp Ser Glu Ala Ala Arg Gly Pro Val Lys Pro Thr Tyr Asn Ser  
130 135 140

Phe Phe Ile Tyr Cys Lys Gly Pro Cys His Lys Val Gln Pro Gly Lys  
145 150 155 160

Leu Arg Val Gln Cys Gly Thr Cys Lys Gln Ala Thr Leu Thr Leu Ala  
165 170 175

Gln Gly Pro Ser Cys Trp Asp Asp Val Leu Ile Pro Asn Arg Met Ser  
180 185 190

Gly Glu Cys Gln Ser Pro Asp Cys Pro Gly Thr Arg Ala Glu Phe Phe  
195 200 205

Phe Lys Cys Gly Ala His Pro Thr Ser Asp Lys Asp Thr Ser Val Ala  
210 215 220

Leu Asn Leu Ile Thr Ser Asn Arg Arg Ser Ile Pro Cys Ile Ala Cys  
225 230 235 240

Thr Asp Val Arg Ser Pro Val Leu Val Phe Gln Cys Asn His Arg His  
245 250 255

Val Ile Cys Leu Asp Cys Phe His Leu Tyr Cys Val Thr Arg Leu Asn  
260 265 270

Asp Arg Gln Phe Val His Asp Ala Gln Leu Gly Tyr Ser Leu Pro Cys  
275 280 285

Val Val Cys Phe Leu Pro Gly Leu  
290 295

<210> 28  
<211> 37  
<212> PRT  
<213> mouse

<400> 28  
Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu

1 5 10 15

Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
20 25 30

Arg Arg Gly Ser Ser  
35

<210> 29  
<211> 53  
<212> PRT  
<213> mouse

<400> 29  
Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
1 5 10 15

Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
20 25 30

Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
35 40 45

Glu Leu Pro Ile Thr  
50

<210> 30  
<211> 77  
<212> PRT  
<213> mouse

<400> 30  
Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
1 5 10 15

Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
20 25 30

Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
35 40 45

Glu Leu Pro Asn His Leu Thr Val Gln Asn Cys Asp Leu Glu Gln Gln  
50 55 60

Ser Ile Val His Ile Val Gln Arg Pro Arg Glu Lys Ser  
65 70 75

<210> 31  
<211> 14  
<212> PRT  
<213> mouse

<400> 31  
Met Ile Val Thr Val Thr Trp Asn Asn Arg Val Leu Tyr Thr  
1 5 10

<210> 32  
<211> 464  
<212> PRT  
<213> mouse

<400> 32  
Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
1 5 10 15

Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
20 25 30

Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
35 40 45

Glu Leu Pro Asn His Leu Thr Val Gln Asn Cys Asp Leu Glu Gln Gln  
50 55 60

Ser Ile Val His Ile Val Gln Arg Pro Arg Arg Arg Ser His Glu Thr  
65 70 75 80

Asn Ala Ser Gly Gly Asp Glu Pro Gln Ser Thr Ser Glu Gly Ser Ile  
85 90 95

Trp Glu Ser Arg Ser Leu Thr Arg Val Asp Leu Ser Ser His Thr Leu  
100 105 110

Pro Val Asp Ser Val Gly Leu Ala Val Ile Leu Asp Thr Asp Ser Lys  
115 120 125

Arg Asp Ser Glu Ala Ala Arg Gly Pro Val Lys Pro Thr Tyr Asn Ser  
130 135 140

Phe Phe Ile Tyr Cys Lys Gly Pro Cys His Lys Val Gln Pro Gly Asn  
145 150 155 160

Leu Arg Val Gln Cys Gly Thr Cys Lys Gln Ala Thr Leu Thr Leu Ala  
165 170 175

Gln Gly Pro Ser Cys Trp Asp Asp Val Leu Ile Pro Asn Arg Met Ser  
180 185 190

Gly Glu Cys Gln Ser Pro Asp Cys Pro Gly Thr Arg Ala Glu Phe Phe  
195 200 205

Phe Lys Cys Gly Ala His Pro Thr Ser Asp Lys Asp Thr Ser Val Ala  
210 215 220

Leu Asn Leu Ile Thr Ser Asn Arg Arg Ser Ile Pro Cys Ile Ala Cys  
225 230 235 240

Thr Asp Val Arg Ser Pro Val Leu Val Phe Gln Cys Asn His Arg His  
245 250 255

Val Ile Cys Leu Asp Cys Phe His Leu Tyr Cys Val Thr Arg Leu Asn  
260 265 270

Asp Arg Gln Phe Val His Asp Ala Gln Leu Gly Tyr Ser Leu Pro Cys  
275 280 285

Val Ala Gly Cys Pro Asn Ser Leu Ile Lys Glu Leu His His Phe Arg  
290 295 300

Ile Leu Gly Glu Glu Gln Tyr Thr Arg Tyr Gln Gln Tyr Gly Ala Glu  
305 310 315 320

Glu Cys Val Leu Gln Met Gly Gly Val Leu Cys Pro Arg Pro Gly Cys  
325 330 335

Gly Ala Gly Leu Leu Pro Glu Gln Gly Gln Arg Lys Val Thr Cys Glu  
340 345 350

Gly Gly Asn Gly Leu Gly Cys Gly Phe Val Phe Cys Arg Asp Cys Lys  
355 360 365

Glu Ala Tyr His Glu Gly Asp Cys Asp Ser Leu Leu Glu Pro Ser Gly  
370 375 380

Ala Thr Ser Gln Ala Tyr Arg Val Asp Lys Arg Ala Ala Glu Gln Ala  
385 390 395 400

Arg Trp Glu Glu Ala Ser Lys Glu Thr Ile Lys Lys Thr Thr Lys Pro  
405 410 415

Cys Pro Arg Cys Asn Val Pro Ile Glu Lys Asn Gly Gly Cys Met His  
420 425 430

Met Lys Cys Pro Gln Pro Gln Cys Lys Leu Glu Trp Cys Trp Asn Cys  
435 440 445

Gly Cys Glu Trp Asn Arg Ala Cys Met Gly Asp His Trp Phe Asp Val  
450 455 460

<210> 33  
<211> 464  
<212> PRT  
<213> mouse

<400> 33  
Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
1 5 10 15

Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
20 25 30

Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
35 40 45

Glu Leu Pro Asn His Leu Thr Val Gln Asn Cys Asp Leu Glu Gln Gln  
50 55 60

Ser Ile Val His Ile Val Gln Arg Pro Arg Arg Arg Ser His Glu Thr  
65 70 75 80

Asn Ala Ser Gly Gly Asp Glu Pro Gln Ser Thr Ser Glu Gly Ser Ile  
85 90 95

Trp Glu Ser Arg Ser Leu Thr Arg Val Asp Leu Ser Ser His Thr Leu  
100 105 110

Pro Val Asp Ser Val Gly Leu Ala Val Ile Leu Asp Thr Asp Ser Lys  
115 120 125

Arg Asp Ser Glu Ala Ala Arg Gly Pro Val Lys Pro Thr Tyr Asn Ser  
130 135 140

Phe Phe Ile Tyr Cys Lys Gly Pro Cys His Lys Val Gln Pro Gly Lys  
145 150 155 160

Leu Arg Val Gln Cys Gly Thr Cys Lys Gln Ala Thr Leu Thr Leu Ala  
165 170 175

Gln Gly Pro Ser Cys Trp Asp Asp Val Leu Ile Pro Asn Arg Met Ser  
180 185 190

Gly Glu Cys Gln Ser Pro Asp Cys Pro Gly Thr Arg Ala Glu Phe Phe  
195 200 205

Phe Lys Cys Gly Ala His Pro Thr Ser Asp Lys Asp Thr Ser Val Ala  
210 215 220

Leu Asn Leu Ile Thr Ser Asn Arg Arg Ser Ile Pro Cys Ile Ala Cys  
225 230 235 240

Thr Asp Val Arg Ser Pro Val Leu Val Phe Gln Cys Asn His Arg His  
245 250 255

Val Ile Cys Leu Asp Cys Phe His Leu Tyr Cys Val Thr Arg Leu Asn  
260 265 270

Asp Arg Gln Phe Val His Asp Ala Gln Leu Gly Tyr Ser Leu Pro Cys  
275 280 285

Val Ala Gly Cys Pro Asn Ser Leu Ile Lys Glu Leu His His Phe Arg  
290 295 300

Ile Leu Gly Glu Glu Gln Tyr Thr Arg Tyr Gln Gln Tyr Gly Ala Glu  
305 310 315 320

Glu Cys Val Leu Gln Met Gly Val Leu Cys Pro Arg Pro Gly Cys  
325 330 335

Gly Ala Gly Leu Leu Pro Glu Gln Gly Gln Arg Lys Val Thr Cys Glu  
340 345 350

Gly Gly Asn Gly Leu Gly Cys Gly Phe Val Phe Cys Arg Asp Cys Lys  
355 360 365

Glu Ala Tyr His Glu Gly Asp Cys Asp Ser Leu Leu Glu Pro Ser Gly  
370 375 380

Ala Thr Ser Gln Ala Tyr Arg Val Asp Lys Arg Ala Ala Glu Gln Ala  
385 390 395 400

Arg Trp Glu Glu Ala Ser Lys Glu Thr Ile Lys Lys Thr Asn Lys Pro  
405 410 415

Cys Pro Arg Cys Asn Val Pro Ile Glu Lys Asn Gly Gly Cys Met His  
 420                                   425                           430

Met Lys Cys Pro Gln Pro Gln Cys Lys Leu Glu Trp Cys Trp Asn Cys  
 435                                   440                           445

Gly Cys Glu Trp Asn Arg Ala Cys Met Gly Asp His Trp Phe Asp Val  
 450                                   455                           460

<210> 34  
<211> 451  
<212> PRT  
<213> mouse

<400> 34  
Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
 1                                   5                               10                           15

Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
 20                                   25                               30

Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
 35                                   40                               45

Glu Leu Pro Asn His Leu Thr Val Gln Asn Cys Asp Leu Glu Gln Gln  
 50                                   55                               60

Ser Ile Val His Ile Val Gln Arg Pro Arg Arg Arg Ser His Glu Thr  
 65                                   70                               75                           80

Asn Ala Ser Gly Gly Asp Glu Pro Gln Ser Thr Ser Glu Gly Ser Ile  
 85                                   90                               95

Trp Glu Ser Arg Ser Leu Thr Arg Val Asp Leu Ser Ser His Thr Leu  
 100                                   105                           110

Pro Val Asp Ser Val Gly Leu Ala Val Ile Leu Asp Thr Asp Ser Lys  
 115                                   120                           125

Arg Asp Ser Glu Ala Ala Arg Gly Pro Val Lys Pro Thr Tyr Asn Ser  
 130                                   135                           140

Phe Phe Ile Tyr Cys Lys Gly Pro Cys His Lys Val Gln Pro Gly Lys

145                    150                    155                    160  
Leu Arg Val Gln Cys Gly Thr Cys Lys Gln Ala Thr Leu Thr Leu Ala  
165                    170                    175  
Gln Gly Pro Ser Cys Trp Asp Asp Val Leu Ile Pro Asn Arg Met Ser  
180                    185                    190  
Gly Glu Cys Gln Ser Pro Asp Cys Pro Gly Thr Arg Ala Glu Phe Phe  
195                    200                    205  
Phe Lys Cys Gly Ala His Pro Thr Ser Asp Lys Asp Thr Ser Val Ala  
210                    215                    220  
Leu Asn Leu Ile Thr Ser Asn Arg Arg Ser Ile Pro Cys Ile Ala Cys  
225                    230                    235                    240  
Thr Asp Val Arg Ser Pro Val Leu Val Phe Gln Cys Asn His Arg His  
245                    250                    255  
Val Ile Cys Leu Asp Cys Phe His Leu Tyr Cys Val Thr Arg Leu Asn  
260                    265                    270  
Asp Arg Gln Phe Val His Asp Ala Gln Leu Gly Tyr Ser Leu Pro Cys  
275                    280                    285  
Val Ala Gly Cys Pro Asn Ser Leu Ile Lys Glu Leu His His Phe Arg  
290                    295                    300  
Ile Leu Gly Glu Glu Gln Tyr Thr Arg Tyr Gln Gln Tyr Gly Ala Glu  
305                    310                    315                    320  
Glu Cys Val Leu Gln Met Gly Gly Val Leu Cys Pro Arg Pro Gly Cys  
325                    330                    335  
Gly Ala Gly Leu Leu Pro Glu Gln Gly Gln Arg Lys Val Thr Cys Glu  
340                    345                    350  
Gly Gly Asn Gly Leu Gly Cys Gly Phe Val Phe Cys Arg Asp Cys Lys  
355                    360                    365  
Glu Ala Tyr His Glu Gly Asp Cys Asp Ser Leu Leu Glu Pro Ser Gly  
370                    375                    380  
Ala Thr Ser Gln Ala Tyr Arg Val Asp Lys Arg Ala Ala Glu Gln Ala  
385                    390                    395                    400  
Arg Trp Glu Glu Ala Ser Lys Glu Thr Ile Lys Lys Thr Thr Lys Pro

405

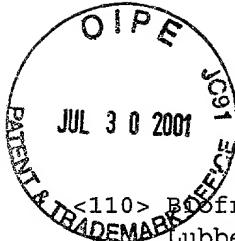
410

415

Cys Pro Arg Cys Asn Val Pro Ile Glu Lys Asn Gly Gly Cys Met His  
420 425 430

Met Lys Cys Pro Gln Pro Gln Cys Lys Leu Glu Trp Cys Trp Asn Cys  
435 440 445

Gly Cys Glu  
450



## SEQUENCE LISTING

<110> Biofrontera Pharmaceuticals AG  
Lubbert, Hermann

<120> TRANSGENIC ANIMAL MODEL FOR  
NEURODEGENERATIVE DISEASES

<130> STERN1.001APC

<140> 09/830,703  
<141> 2001-04-26

<150> EP 99116766.9  
<151> 1999-08-30

<160> 34

<170> FastSEQ for Windows Version 4.0

<210> 1

<211> 3255

<212> DNA

<213> Mus musculus

<400> 1

ctcagcgagg ggaaggggga ggaggccctgg atgactaaac ctgacagaaaa cgctgggtggg 60  
aggctcgggc gggcgccagt gcccgcgtag gtccttctcg acccgccagcc accacccgcc 120  
cggtgaccat gatagtgttt gtcagggttca actccagcta tggcttccca gtggaggtcg 180  
attctgacac cagcatcttg cagctcaagg aagtgggtgc taagcgacag ggggttccag 240  
ctgaccagct gcgtgtgatt tttgccggga aggagcttcc gaatcacctg acggttcaaa 300  
actgtgacct ggaacaacag agtattgtac acatagtaca gagaccacgg aggagaagtc 360  
atgaaacaaa tgcacatcttgc ggggacgaaac cccagagcac ctcagagggc tccatatggg 420  
agtccaggag cttgacacga gtggacctga gcagccatac cctgcccgtg gactctgtgg 480  
ggctggcggt cattctggac acagacagta agagggattc agaagcagcc agaggtccag 540  
ttaaaccac ctacaacacgc ttttcatct actgcaaagg cccctgccac aaggtccagc 600  
ctggaaagct ccgagttcag tgtggcacct gcaaaacaagg aaccctcacc ttggcccagg 660  
gccccatcttgc ctggacatgt gtcttaattt caaacggat gagtgggttag tgccagtctc 720  
cagactgccc tggaaaccaga gctgaatttt tctttaaatg tggagcacac ccaacctcag 780  
acaaggacac gtccgttagct ttgaacctga tcaccagcaa caggcgcagc atcccttgca 840  
tagcgtgcac agatgtcagg agccctgtcc tggcttcca gtgttaaccac cgtcacgtga 900  
tctgtttggc ctgtttccac ttgtattgtc tcacaagact caacgatcgg cagtttgtcc 960  
acgatgctca acttggctac tccctgcgt gttagctgg ctgtcccaac tccctgatta 1020  
aagagctcca tcacttcagg atcccttggag aagagcagta cactaggtac cagcagtatg 1080  
gggccgagga atgcgtgtc caaatggag gtgtgtgtg ccccccgtcct ggctgtggag 1140  
ctggactgtc acctgaacag ggccagagga aagtccacctg cgaagggggc aacggcctgg 1200  
gctgcgggtt tggtttctgc cgggactgtc aggaagcata ccatgaaggg gattgcgact 1260  
caactgcgtca accctcagga gccacttctc aggctacag ggtggacaaa agagccgctg 1320  
agcaagctcg ctgggaggag gcctccaagg aaaccatcaa gaagaccacc aacgcctgtc 1380  
ctcgctgcaa cgtgccaatt gaaaaaaaaacg gaggatgtat gcacatgaag tgcctcagc 1440  
cccagtgcac gctggagtg gtcgttgcact gtggctgtga gtggacccga gcctgcattgg 1500  
gagatcactg gtttgacgtg tagagagaga tgcacttgg ccctggacgc acaacctcaa 1560  
gggaaactcc gaagattcct accttcctta gccatttctt cttctcgatg catataagca 1620  
cataaatgcg cacacacaaa cacaggctgc agattacaga agcagccccct agatccttcc 1680

tagggcaccc acagaaaacc acagcacccg ctggccccag ggggaggagg cactttcagc 1740  
ctctggctca ctcgaatgtc agagcttaga tgagggtgca ccttgggtt ggattctgta 1800  
gaagccatga gtgaggtggg aagtgtttc caggggtgtt gccacgcctt ggtaagtaa 1860  
cacctctgag gattctcaga agcacactt agatctgagg aacgctgctc tcatgttagta 1920  
atcatctatt cccaaagggc cccctgcagt agtcaaaact atttgtttat ccccccataat 1980  
cctatctta caaatggtgc ttagatgagatt acaacccctc tggactaa tcagcttatac 2040  
aaccgaatgtga gaaccttagga aagctaattt gatggcagac tgcttaatc gcagggagga 2100  
ctcagaagcc aaacctactt ccgttcgtt cattatctgc aacttttagaa agaaatgatc 2160  
ttttttccc cctgaaaaga taacaaagtc tgcaatttg tttggagtt tcctactgca 2220  
gcctggaagt tttagttcac tgtgaattt acagagaaag tgcctataaaa gggggcggtt 2280  
ttaagagaca atcccatgtat gctgcgcca tgcttaacaac agggtcaaga aacacaatgt 2340  
ttatagaagg agcatccctc gaccatctga atgagagtttgc gcctgacccc ttccaccaca 2400  
agtggggaca cctctgcata tctgctccct cctctgtgt taagccccag ggagccccat 2460  
ccacccagtg gtcctacaga cagggcaata cacacacacc aagatagcct tcagatcaac 2520  
atgcatacaca ctcaagtgtt aatcttcaa ggttttctt tctttttctt gttttttatt 2580  
tgttttgctt ttgctttttt tttttttttt tttgggtgtt gtggggctac caaacttgag 2640  
gccttagagct aaaaatcata tagaaaatgtt gttatctgtt ggtgtgagga aaggccagct 2700  
ggcctaagtt cacacttttgc tcccaggcacttcc acccagccag ctcccaaaaat 2760  
gaaaagacca cctgtcaagc agcagtcagg agtctgtatgta caccatcac tttttttttt 2820  
ccatcattgt gcttcctct gcctccttcc acacccgtgt gacgtatcg cattgggaag 2880  
ccaggacaat gtttgcgtt ctgctttggg taaaggact ccctgaagct ctgtggctct 2940  
ccagttatgtt ccctttctt tcctaacaga tgcataatgtt ttcttcagaa tacaatagtg 3000  
attcttaaaa taacccaaaaa gacaggcatc cacagtgtgtt gggatgttccatc 3060  
attgtgtgag tgtgaatagt gggataaaag tggatgtcag aaggtggaa atcaaacctc 3120  
tgcaaagccaa tctttctt tctgtgaatgtt gttttttttt gttttttttt 3180  
tgggtgttacc cagactgtca atcaataaaag acccagactg tcaatgaaaa aaaaaaaaaaa 3240  
aaaaaaaaaaa aaaaaa 3255

<210> 2  
<211> 1459  
<212> DNA  
<213> Mus musculus

<400> 2  
ctcacgggaa ggaggccctt gatgactaaa cctgacagaa acgctggtgg gaggctcgaa 60  
cgggcgcctt tgcccgctt ggtccttcc gaccgcgc caccacccgc ccgggtgacca 120  
tgatagtgtt tgtcagggtt aactccagct atggcttccc agtggagggtt gattctgaca 180  
ccagcatctt gcagctcaag gaagtgggtt ctaagcgaca gggggttcca gctgaccaggc 240  
tgcgtgttat ttttgcggg aaggagttt cgaatcacct gacggttcaa aactgtgacc 300  
tggaacaaca gagtattgtt cacatagttt acagaccacg gaggagaagt catgaaacaa 360  
atgcatactgg aggggacgaa ccccaagagca cctcagaggg ctccatatgg gatccagga 420  
gcttgacacg agtggacccgtt agcagccata ccctgcccgtt ggactctgtt gggctggcg 480  
tcattctgga cacagacagt aagaggattt cagaagcagc cagaggccca gcaatggaa 540  
ccacctacaa cagtttttcc atctactgca aaggcccttgc ccacaaggc cagcctggaa 600  
agctccgagt tcagtgtggc acctgcaaac aagcaaccctt cacccttggcc cagggcccat 660  
cttgctggaa cgatgtctt attccaaacc ggttggatgg tgagtggccag tctccagact 720  
gccctggaaac cagagctgaa tttttcttta aatgtggaggc acacccaaacc tcagacaagg 780  
acacgtcggtt agctttgaac ctgatccca gcaacaggcg cagcatccct tgcatacggt 840  
gcacagatgtt cagtcatctt cctctgtcat ctgggtgcctc cgtgtggact cggcctcatc 900  
tccactgaac cttttttttt aggactgtgc aataggtgtt cacccttac tgagaacaag 960  
gcagcttctg gtctcttggt ttcccttgcctt ccaacggcag cattgactgtt acacccttca 1020  
gtccttaccaa ccccaatttcc tgggttggatttt ctttaccgtt tagcttctcc aagatgccta 1080  
tttccacacca cagtttttg tcttcccat ccccccataat gttttatggcgc attagtaagc 1140  
accgcacccctc attagttgtt gcttctgtata caagacttcc tggatcccc gcttgagccc 1200  
tagaatcccc tggaaactggg ttctgttacc tatcttcaat agcctttttt aaaaatgtgat 1260

tcttgggctg gtgagatggc tcagtggta agagcacccg actgctttc cgaagtccag 1320  
agttcaaaat cccagcaacc acatggtggc tcacaaccat ccgtaacaag atctgactcc 1380  
ctcttctgt gtgtctgaag acagctacag tgtacttaca taaaataata aataaatctt 1440  
aaaaaaaaaaaa aaaaaaaaaa 1459

<210> 3  
<211> 857  
<212> DNA  
<213> Mus musculus

<400> 3  
ctcagatgac taaacctgac agaaacgctg gtgggaggct cgggcgggct ccagtccccg 60  
cgttagtcct tctcgaccgg cagccaccac ccgcgggtg accatgatag tgtttgc 120  
gttcaactcc agctatggct tcccagtgga ggtcgattct gacaccagca tctgcagct 180  
caaggaagtg gttgctaagc gacaggggt tccagctgac cagctgcgtg tgattttgc 240  
cggaaaggag cttccgaatc acctgacggt tcaaaaactgt gacctgaaac aacagagtat 300  
tgtacacata gtacagagac cacggaggag aagtcatgaa acaaattgtat ctggagggga 360  
cgaaccccaag agcacccatc agggctccat atgggatgtc aggagcttga caccaggatg 420  
cctgagcagc cataccctgc cggtggactc tgggggctg gcggtcattc tggacacaga 480  
cagtaagagg gattcagaag cagccagagg tccagcgtt aaacccacat acaacagctt 540  
tttcatctac tgcaaaggcc cctgccacaa ggtccagcct ggaaagctcc gagttcagt 600  
tggcacctgc aaacaagcaa ccctcacctt ggcccaggc ccattttgc gggacgatgt 660  
cttaattcca aaccggatga gtggtgagtg ccagtctcca gactgccctg gaaccagagc 720  
tgaatttttc tttaaatgtg gagcacaccc aacccatgac aaggacacgt cggtagctt 780  
gaacctgatc accagcaaca ggccgcagcat ccctgcata gcgtgcacag atgtcagggtt 840  
tatgcgcatg agttac 857

<210> 4  
<211> 464  
<212> PRT  
<213> Mus musculus

<400> 4  
Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
1 5 10 15  
Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
20 25 30  
Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
35 40 45  
Glu Leu Pro Asn His Leu Thr Val Gln Asn Cys Asp Leu Glu Gln Gln  
50 55 60  
Ser Ile Val His Ile Val Gln Arg Pro Arg Arg Arg Ser His Glu Thr  
65 70 75 80  
Asn Ala Ser Gly Gly Asp Glu Pro Gln Ser Thr Ser Glu Gly Ser Ile  
85 90 95  
Trp Glu Ser Arg Ser Leu Thr Arg Val Asp Leu Ser Ser His Thr Leu  
100 105 110  
Pro Val Asp Ser Val Gly Leu Ala Val Ile Leu Asp Thr Asp Ser Lys  
115 120 125  
Arg Asp Ser Glu Ala Ala Arg Gly Pro Val Lys Pro Thr Tyr Asn Ser  
130 135 140  
Phe Phe Ile Tyr Cys Lys Gly Pro Cys His Lys Val Gln Pro Gly Lys  
145 150 155 160  
Leu Arg Val Gln Cys Gly Thr Cys Lys Gln Ala Thr Leu Thr Leu Ala  
165 170 175

Gln Gly Pro Ser Cys Trp Asp Asp Val Leu Ile Pro Asn Arg Met Ser  
                  180                 185                 190  
 Gly Glu Cys Gln Ser Pro Asp Cys Pro Gly Thr Arg Ala Glu Phe Phe  
                  195                 200                 205  
 Phe Lys Cys Gly Ala His Pro Thr Ser Asp Lys Asp Thr Ser Val Ala  
                  210                 215                 220  
 Leu Asn Leu Ile Thr Ser Asn Arg Arg Ser Ile Pro Cys Ile Ala Cys  
                  225                 230                 235                 240  
 Thr Asp Val Arg Ser Pro Val Leu Val Phe Gln Cys Asn His Arg His  
                  245                 250                 255  
 Val Ile Cys Leu Asp Cys Phe His Leu Tyr Cys Val Thr Arg Leu Asn  
                  260                 265                 270  
 Asp Arg Gln Phe Val His Asp Ala Gln Leu Gly Tyr Ser Leu Pro Cys  
                  275                 280                 285  
 Val Ala Gly Cys Pro Asn Ser Leu Ile Lys Glu Leu His His Phe Arg  
                  290                 295                 300  
 Ile Leu Gly Glu Glu Gln Tyr Thr Arg Tyr Gln Gln Tyr Gly Ala Glu  
                  305                 310                 315                 320  
 Glu Cys Val Leu Gln Met Gly Gly Val Leu Cys Pro Arg Pro Gly Cys  
                  325                 330                 335  
 Gly Ala Gly Leu Leu Pro Glu Gln Gly Gln Arg Lys Val Thr Cys Glu  
                  340                 345                 350  
 Gly Gly Asn Gly Leu Gly Cys Gly Phe Val Phe Cys Arg Asp Cys Lys  
                  355                 360                 365  
 Glu Ala Tyr His Glu Gly Asp Cys Asp Ser Leu Leu Glu Pro Ser Gly  
                  370                 375                 380  
 Ala Thr Ser Gln Ala Tyr Arg Val Asp Lys Arg Ala Ala Glu Gln Ala  
                  385                 390                 395                 400  
 Arg Trp Glu Glu Ala Ser Lys Glu Thr Ile Lys Lys Thr Thr Lys Pro  
                  405                 410                 415  
 Cys Pro Arg Cys Asn Val Pro Ile Glu Lys Asn Gly Gly Cys Met His  
                  420                 425                 430  
 Met Lys Cys Pro Gln Pro Gln Cys Lys Leu Glu Trp Cys Trp Asn Cys  
                  435                 440                 445  
 Gly Cys Glu Trp Asn Arg Ala Cys Met Gly Asp His Trp Phe Asp Val  
                  450                 455                 460

<210> 5  
 <211> 262  
 <212> PRT  
 <213> Mus musculus

<400> 5  
 Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
     1              5                 10                 15  
 Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
     20             25                 30  
 Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
     35             40                 45  
 Glu Leu Pro Asn His Leu Thr Val Gln Asn Cys Asp Leu Glu Gln Gln  
     50             55                 60  
 Ser Ile Val His Ile Val Gln Arg Pro Arg Arg Arg Ser His Glu Thr  
     65             70                 75                 80  
 Asn Ala Ser Gly Gly Asp Glu Pro Gln Ser Thr Ser Glu Gly Ser Ile

| 85  | 90  | 95      |
|---|-----|---------|
| Trp Glu Ser Arg Ser Leu Thr Arg Val Asp Leu Ser Ser His         |     | Thr Leu |
| 100   | 105 | 110     |
| Pro Val Asp Ser Val Gly Leu Ala Val Ile Leu Asp Thr Asp Ser Lys |     |         |
| 115   | 120 | 125     |
| Arg Asp Ser Glu Ala Ala Arg Gly Pro Ala Val Lys Pro Thr Tyr Asn |     |         |
| 130   | 135 | 140     |
| Ser Phe Phe Ile Tyr Cys Lys Gly Pro Cys His Lys Val Gln Pro Gly |     |         |
| 145   | 150 | 155     |
| Lys Leu Arg Val Gln Cys Gly Thr Cys Lys Gln Ala Thr Leu Thr Leu |     |         |
| 165   | 170 | 175     |
| Ala Gln Gly Pro Ser Cys Trp Asp Asp Val Leu Ile Pro Asn Arg Met |     |         |
| 180   | 185 | 190     |
| Ser Gly Glu Cys Gln Ser Pro Asp Cys Pro Gly Thr Arg Ala Glu Phe |     |         |
| 195   | 200 | 205     |
| Phe Phe Lys Cys Gly Ala His Pro Thr Ser Asp Lys Asp Thr Ser Val |     |         |
| 210   | 215 | 220     |
| Ala Leu Asn Leu Ile Thr Ser Asn Arg Arg Ser Ile Pro Cys Ile Ala |     |         |
| 225   | 230 | 235     |
| Cys Thr Asp Val Ser His Leu Pro Leu Ser Ser Gly Ala Ser Val Trp |     |         |
| 245   | 250 | 255     |
| Thr Arg Pro His Leu His   |     |         |
| 260   |     |         |

<210> 6  
<211> 250  
<212> PRT  
<213> Mus musculus

|   |     |     |     |
|---|-----|-----|-----|
| <400> 6   |     |     |     |
| Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu |     |     |     |
| 1   | 5   | 10  | 15  |
| Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys |     |     |     |
| 20  | 25  | 30  |     |
| Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys |     |     |     |
| 35  | 40  | 45  |     |
| Glu Leu Pro Asn His Leu Thr Val Gln Asn Cys Asp Leu Glu Gln Gln |     |     |     |
| 50  | 55  | 60  |     |
| Ser Ile Val His Ile Val Gln Arg Pro Arg Arg Arg Ser His Glu Thr |     |     |     |
| 65  | 70  | 75  | 80  |
| Asn Ala Ser Gly Gly Asp Glu Pro Gln Ser Thr Ser Glu Gly Ser Ile |     |     |     |
| 85  | 90  | 95  |     |
| Trp Glu Ser Arg Ser Leu Thr Arg Val Asp Leu Ser Ser His Thr Leu |     |     |     |
| 100   | 105 | 110 |     |
| Pro Val Asp Ser Val Gly Leu Ala Val Ile Leu Asp Thr Asp Ser Lys |     |     |     |
| 115   | 120 | 125 |     |
| Arg Asp Ser Glu Ala Ala Arg Gly Pro Ala Val Lys Pro Thr Tyr Asn |     |     |     |
| 130   | 135 | 140 |     |
| Ser Phe Phe Ile Tyr Cys Lys Gly Pro Cys His Lys Val Gln Pro Gly |     |     |     |
| 145   | 150 | 155 | 160 |
| Lys Leu Arg Val Gln Cys Gly Thr Cys Lys Gln Ala Thr Leu Thr Leu |     |     |     |
| 165   | 170 | 175 |     |
| Ala Gln Gly Pro Ser Cys Trp Asp Asp Val Leu Ile Pro Asn Arg Met |     |     |     |
| 180   | 185 | 190 |     |

Ser Gly Glu Cys Gln Ser Pro Asp Cys Pro Gly Thr Arg Ala Glu Phe  
 195 200 205  
 Phe Phe Lys Cys Gly Ala His Pro Thr Ser Asp Lys Asp Thr Ser Val  
 210 215 220  
 Ala Leu Asn Leu Ile Thr Ser Asn Arg Arg Ser Ile Pro Cys Ile Ala  
 225 230 235 240  
 Cys Thr Asp Val Arg Phe Met Arg Met Ser  
 245 250

<210> 7

<211> 3014

<212> DNA

<213> Mus musculus

<400> 7

ctcagcgagg ggaaggggga ggaggcctgg atgactaaac ctgacagaaa cgctggtggg 60  
 aggctcgggc gggcgccagt gcccgcgtag gtccttctcg acccgcagcc accacccgcc 120  
 cggtgaccat gatagtgttt gtcagggttca actccagcta tggcttccca gtggaggtcg 180  
 attctgacac cagcatcttg cagctcaagg aagtggttgc taagcgacag ggggttccag 240  
 ctgaccagct gcgtgtgatt ttggccggga aggagcttcc gaatcacctg acggttcaat 300  
 taaaacccacc tacaacagct ttttcatcta ctgcaaaggc ccctgcccaca aggtccagcc 360  
 tggaaagctc cgagttcagt gtggcacctg caaacaagca accctcacct tggcccaggg 420  
 cccatcttgc tgggacgatg tcttaattcc aaaccggatg agtggtgagt gccagtctcc 480  
 agactgcct ggaaccagag ctgaattttt cttaaatgt ggagcacacc caaccctcaga 540  
 caaggacacg tcggtagctt tgaacctgtat caccagcaac aggcgcagca tcccttgcatt 600  
 agcgtgcaca gatgtcagga gcccgtcctt ggtcttccag tgtaaccacc gtacacgttat 660  
 ctgtttggac tgtttccact tgtagttgtt cacaagactc aacgatcgcc agtttgtcca 720  
 cgatgctcaa cttggctact ccctgcccgtg tgtagctggc tgtcccaact ccctgattaa 780  
 agagctccat cacttcagga tccttggaga agagcagttt actaggttacc agcagtatgg 840  
 ggccgaggaa tgcgtgctgc aaatgggagg tggctgtgc cccctcctg gctgtggagc 900  
 tggactgcta cctgaacagg gcccaggaa agtcacactgc gaaggggca acggcctggg 960  
 ctgcgggtt gtttctgcc gggactgtaa ggaagcatac catgaagggg attgcactc 1020  
 actgctcgaa ccctcaggag ccacttctca ggcctacagg gtggacaaaa gagccgctga 1080  
 gcaagctcgc tgggaggagg cctccaagga aaccatcaag aagaccacca agccttgc 1140  
 tcgctgcaac gtggccaattt aaaaaaaaaacgg aggatgtatg cacaatgtt gtcctcagcc 1200  
 ccagtgcaag ctggagtgg tggactgttgg tggactgttgg tggactgttgg cctgcatggg 1260  
 agatcaactgg tttgacgtgtt agagagagat gtcacttggc cctggacgca caacctcaag 1320  
 gggaaactccg aagattcccta cttcccttag ccatttcttc ttctcgatgc atataagcac 1380  
 ataaatgcgc acacacaaac acaggctgca gattacagaa gcagcccccta gatcccttct 1440  
 agggcaccca cagaaaaacca cagcaccgc tggcccccagg gggaggaggc actttcagcc 1500  
 tctggctcac tcgaatgtca gagcttagat gagggtgcac ctttggtttg gattctgttag 1560  
 aagccatgag tgaggtggg agtggttcc aggtttgtt ccacgcctg ggttaagtaac 1620  
 acctctgagg attctcagaa gcacacttgc gatctgagga acgctgtct catgttagaa 1680  
 tcatctattt ccaaaggggcc ccctgcagta gtcaaaaacta ttgttttata ccccaaatac 1740  
 ctatcttac aaatgggtct gatgagatca caacccctct gtgtactaat cagcttatca 1800  
 accaagtgag aacctaggaa agctaattgg atggcagact gcttaaatcg cagggaggac 1860  
 tcagaagccca aacctacttc cgttcggttc attatctgca acttttagaaa gaaatgatct 1920  
 tttttccccctt ctgaaaaagat aacaaagtct gcaatttggt ttggagttt cctactgcag 1980  
 cctggaaaggtagt ttggatctt gtaattaa cagagaaaagg gcctataaaag ggggcgtttt 2040  
 taagagacaa tcccatgatg ctgcgcctt gctaaacaaca gggtaagaa acacaatgtt 2100  
 tatagaagga gcatccctcg accatctgaa tgaggtatg cctgaccctt tccaccacaa 2160  
 gtggggacac ctctgcataat ctgctccctc ctctgctgtt aagcccccagg gagccccatc 2220  
 caccctgg tccctacagac agggcaatac acacacacca agatagcctt cagatcaaca 2280  
 tgcacacac tcaagtgtt atcttcaag gttttttttt cttttccctg ttttttattt 2340

gttttgcctt tgctttttt ttttttttt ttgggtggg tggggctacc aaacttgagg 2400  
cctagagcta aaaatcatat agaaatgatg ttatcttgc gtgtgaggaa aggcagctg 2460  
gcctaagtcc acacccatgt cccagtgcc ctagactcca cccagccagc tcccaaaatg 2520  
aaaagaccac ctgtcaagca gcagtcagga gtctgatgtc accccatcaact atttttttc 2580  
catcattgtg cttgcctctg cctccttcca caccctgtg acgtaatcg attggaaagc 2640  
caggacaatg tttgtctgtc tgctttgggt aaaggactc cctgaagctc tgtggctctc 2700  
cagtatggc cctttccctt cctaacagat gcatatgttt tcttcagaat acaatagtga 2760  
ttcttaaat aacccaaag acaggcatcc acagtgtgtg agcatgaatc acagcctgca 2820  
ttgtgtgagt gtgaatagtg ggataaaaagt ggatgtcaga agagtggaaa tcaaacctct 2880  
gcaaagcaat ctttctctt ctgtgaagtg tattaagaaa tacctgaagt ctgtgtgt 2940  
ggtgttaccc agactgtcaa tcaataaaga cccagactgt caatgaaaaa aaaaaaaaaa 3000  
aaaaaaaaaa aaaa 3014

<210> 8  
<211> 2895  
<212> DNA  
<213> Mus musculus

<400> 8  
ctcagcgagg ggaaggggga ggaggcctgg atgactaaac ctgacagaaa cgctggtggg 60  
aggctcgccc gggcgccagt gcccgcgtag gtccttctcg accccgcagcc accacccgcc 120  
cggtgaccat gatagtgtt gtcaggttca actccagcta tggcttccca gtggaggtcg 180  
attctgacac cagcatctg cagctcaagg aagtgggtgc taagcgacag ggggttccag 240  
ctgaccagct gcgtgtgatt tttgccggg aggagctcc gaatcacctg acggttcaag 300  
gccccatctt ctgggacgt gtcttaattt caaaccggat gagtgggtgag tgccagtc 360  
cagactgccc tggAACAGA gctgaatttt tctttaaatg tggagcacac ccaacacctcg 420  
acaaggacac gtcggtagct ttgaacctga tcaccagcaa caggcgcagc atcccttgca 480  
tagcgtgcac agatgtcagg agccctgtcc tggcttcca gtgttaaccac cgtcacgtga 540  
tctgtttggg ctgtttccac ttgttattgtg tcacaagact caacgatcgg cagtttgc 600  
acgatgctca acttggctac tccctgcgt gttagctgg ctgtcccaac tccctgatta 660  
aagagctcca tcacttcagg atccttgag aagagcagta cactaggtac cagcagtatg 720  
gggcccgggaa atgcgtgtg caaatggggag gtgtgctgtg ccccccgtctt ggctgtggag 780  
ctggactgtc acctgaacag ggccagagga aagtccacctg cgaagggggc aacggcctgg 840  
gctgcgggtt tggtttctgc cgggactgta aggaagcata ccatgaaggg gattgcact 900  
caactgcgtca accctcaggaa gccacttctc aggctacag ggtggacaaa agagccgctg 960  
agcaagctcg ctgggaggag gcctccaagg aaaccatcaa gaagaccacc aacgccttgc 1020  
ctcgctgcaaa cgtgccaatt gaaaaaaaaacg gaggatgtat gcacatgaag tgcctcago 1080  
cccagtgc当地 gctggagtgg tgcttggact gtggctgtga gtggacccga gcctgc当地gg 1140  
gagatcactg gtttgc当地tg tagagagaga tgctacttgg ccctggacgc acaacctcaa 1200  
gggaaactcc gaagattcc accttccctt gccatttctt cttctcgatg catataagca 1260  
cataaaatgc当地 cacacacaaa cacaggctgc agattacaga agcagccct agatccttgc 1320  
tagggcaccc acagaaaaacc acagcacccg ctggccccag ggggaggagg cacttccago 1380  
ctctggctca ctcgaatgtc agagctttaga tgagggtgca cctttgggtt ggattctgt 1440  
gaagccatga gtgagggtggg aagtgtttc cagggttggt gccacccctt gggtaagtaa 1500  
cacctctgag gattctcaga agcacactt agatctgagg aacgctgctc tcatgttagta 1560  
atcatctatt cccaaaggcc cccctgc当地gt agtcaaaact atttgtttt ccccccaat 1620  
cctatctt caaatgggtgc tgatgagatt acaacccctc tgc当地tactaa tcagcttata 1680  
aaccaagtga gaaccttaga aagctaaattt gatggcagac tgctt当地atc gcaggggagga 1740  
ctcagaagcc aaacctactt ccgttgc当地t cattatctgc aacttttagaa agaaatgtc 1800  
ttttttccctt cctgaaaaga taacaaatgc tgcaatttgg tttggaggat tgc当地tactgca 1860  
gcctggaaatg ttagcttccac tgc当地tattt acagagaaaag tgc当地tataaa gggggcgttt 1920  
ttaagagagaca atcccatgt gctgc当地ccaa tgctt当地acaac agggtcaaga aacacaatgt 1980  
ttatagaagg agcatccctc gaccatctga atgagagat gctgacccccc ttccaccaca 2040  
agtggggaca cctctgc当地t tctgctccctt cctctgctgt taagccccag ggagccccat 2100  
ccacccaggc gtccttacaga caggc当地ataa cacacacacc aagatgc当地t tcagatcaac 2160

atgcatcaca ctcaagtgtt aatctttcaa ggaaaaatcc ttttttcc ttttttttt gttttttatt 2220  
tgaaaaatcc ttggccatcc tttttttttt tttgggtggg gtggggctac caaaactttag 2280  
gccttagatc aaaaatcata tagaaatgtat gttatcttgc ggtgtgagga aaggccagct 2340  
ggcctaagtt cacaccccccc tcccaggcgc cctagactcc accccagccag ctcccaaaat 2400  
gaaaagacca cctgtcaagc agcagtcagg agtctgtatgt cacccatcac tttttttttt 2460  
ccatcattgt gcttgcctct gcctccctcc acacccgtgt gacgtaatcg cattgggaag 2520  
ccaggacaat gtttgcgtt ctgctttggg taaaggact ccctgaagct ctgtggctct 2580  
ccagtatgtt ccctttcc tcctaacaga tgcatatgtt ttcttcagaa tacaatagtg 2640  
attcttaaaa taacccaaaaa gacaggcatc cacagtgtgt gagcatgaat cacagcctgc 2700  
attgtgtgag tgtgaatagt gggataaaaag tggatgtcag aagagtggaa atcaaaccctc 2760  
tgcaaaagccaa tctttcttctt tctgtgaagt gtatataagaa atacctgaag tctgtgtgt 2820  
tgggtgttacc cagactgtca atcaataaaag acccagactg tcaatgaaaaa aaaaaaaaaa 2880  
aaaaaaaaaaa aaaaaa 2895

<210> 9  
<211> 2558  
<212> DNA  
<213> Mus musculus

<400> 9  
ctcagcgagg ggaaggggga ggaggccctgg atgactaaac ctgacagaaaa cgctgggtggg 60  
aggctcgggc gggcgccagt gcccgcgtag gtccttctcg accccgcagcc accacccgcc 120  
cggtgaccat gatagtgttt gtcagggttca actccagcta tggcttccca gtggaggtcg 180  
attctgacac cagcatcttgc cagctcaagg aagtgggtgc taagcgacag ggggttccag 240  
ctgaccagct gcgtgtgatt tttggccggg aggagcttcc gaatcacctg acggttcaac 300  
tggctgtccc aactccctga ttaaaagagct ccatcacttc aggtacccctt gagaagagca 360  
gtacacttagg taccagcagt atggggccga ggaatgcgtg ctgcaaatgg gaggtgtgt 420  
gtgccccctgt cctggctgtg gagctggact gctacctgaa cagggccaga gaaagtcac 480  
ctgcgaagggg ggcaacggcc tgggctgcgg gtttgtttc tgccggact gtaaggaagc 540  
ataccatgaa ggggatttgcg actcactgtc cgaaccctca ggagccactt ctcaggccta 600  
cagggtggac aaaagagccg ctgagcaagc tcgctggag gaggcctcca agggaaaccat 660  
caagaagacc accaaggcctt gtcctcgctg caacgtgcga attaaaaaaa acggaggatg 720  
tatgcacatg aagtgtccctc agccccagtg caagctggag tgggtgttgcg actgtggctg 780  
tgagtggAAC cgagccgtca tgggagatca ctggtttgcg gtgttagagag agatgtcact 840  
tggccctggc cgccacaacctt caagggaaac tccgaagatt cctaccccttcc tttagccattt 900  
cttcttctcg atgcatataa gcacataaaat ggcacacac aaacacaggc tgcagattac 960  
agaagcagcc cctagatcct ttcttagggca cccacagaaaa accacagcac ccgctggccc 1020  
cagggggagg aggcaacttcc agcctctggc tcactcgat gtcagagctt agatgagggt 1080  
gcaccccttgg tttggattct gtagaagccaa tgagtggactt gggaaagtgtt ttccagggtt 1140  
gttgccacgc cctgggttaag taacaccctt gaggattctc agaagcacac ttgagatctg 1200  
aggaacgcgtc ctctcatgtt gtaatcatctt attcccaaaag ggccccctgc agttagtcaaa 1260  
actatTTTtt tatccccccca aatcctatctt ttacaaatgg tgctgtatgag attacaaccc 1320  
ctctgtgtac taatcagctt atcaaccaag tgagaaccta ggaaagctaa ttggatggca 1380  
gactgcttaa atcgcaggga ggactcgaaa gccaaaccta cttccgttgc ttccatttac 1440  
tgcaacttta gaaagaaaatg atctttttt cccctgaaa agataacaaa gtcgtcaattt 1500  
tggtttggag tattccactt gcaaggccctt gatgtgtatgtt cactgtgaat ttaacagaga 1560  
aagtgcctat aaaggggggcg ttttttaagag acaatcccat gatgtgtgcgca caatgctaac 1620  
aacagggtca agaaacacaa tgtttataga aggagcatcc ctcgaccatc tgaatgagag 1680  
tatgcctgtac cccttccacc acaagtgggg acacccctgc atatctgtc cctccctgtc 1740  
tgttaaggccc cagggagccc catccaccca gtggccttac agacaggcga atacacacac 1800  
accaagatag ccttcagatc aacatgcattt acactcaatgtt gttatctt caagggtttc 1860  
ttttctttttt cctgtttttt atttgggtttt cttttgtttt tttttttttt ttttttgggtg 1920  
gtgggtggggc tacccaaactt gaggccctaga gctaaaaatc atatagaaaat gatgttatct 1980  
tgtgggtgtga ggaaaggccaa gctggccctaa gttcacactt ttgtcccagt ggccctagac 2040  
tccacccacgc cagctcccaa aatgaaaaaga ccacccgtca agcagcagtc aggagtctga 2100

tgtcaccat cactatttt tttccatcat tgtgcttgc tctgcctcct tccacacccg 2160  
tgtgacgtaa tcgcattggg aagccaggac aatgtttgct gttctgcctt gggtaaaggg 2220  
actccctgaa gctctgtggc tctccagtat ggtcccttt ctttcctaac agatgcata 2280  
gttttcttca gaatacaata gtgattctta aaataacca aaagacaggg atccacagtg 2340  
tgtgagcatg aatcacagcc tgcattgtgt gagtgtgaat agtgggataa aagtggatgt 2400  
cagaagagtg gaaatcaaac ctctgcaaag caatcttct ctttctgtga agtgtattaa 2460  
gaaataacctg aagtctgtgt gtgtgggtt acccagactg tcaatcaata aagacccaga 2520  
ctgtcaatga aaaaaaaaaaaaaaaa aaaaaaaaaaaaaaaa aaaaaaaaaa 2558

<210> 10

<211> 3136

<212> DNA

<213> Mus musculus

<400> 10

ctcagcgagg ggaaggggga ggaggcctgg atgactaaac ctgacagaaa cgctgggtgg 60  
aggctcgggc gggcgccagt gcccgcgtag gtccttctcg acccgagcc accacccgccc 120  
cggtgaccat gatagtgttt gtcaggttca actccagcta tggctccca gtggaggtcg 180  
attctgacac cagcatctt cagctcaagg aagtgggtgc taagcgacag ggggttccag 240  
ctgaccagct gcgtgtgatt tttgccggg aggagcttcc gaatcacctg acggttcaaa 300  
actgtgacact ggaacaacag agtattgtac acatagtaca gagaccacgg aggagaagtc 360  
atgaaacaaa tgcacatcttgg ggggacgaac cccagagcac ctcagagggc tccatatggg 420  
agtccaggag cttgacacga gtggacctga gcagccatac cctgcccgtg gactctgtgg 480  
ggctggcggt cattctggac acagacagta agagggattc agaagcagcc agaggtccag 540  
ggccccatctt gctgggacga tgcatttaatt ccaaaccggg tgagtggta gtggcagtct 600  
ccagactgcc ctggaaaccag agctgaattt ttctttaat gtggagcaca cccaaacctca 660  
gacaaggaca cgtcggttagc tttgaacctg atcaccagca acaggcgcag catcccttgc 720  
atagcgtgca cagatgtcag gagccctgtc ctggtcttcc agtgaacca ccgtcacgtg 780  
atctgtttgg actgtttcca cttgtattgt gtcacaagac tcaacgatcg gcagttgtc 840  
cacgatgctc aacttggcta ctccctgccc tgcgttagctg gctgtcccaa ctccctgatt 900  
aaagagctcc atcacttcag gatccttgg aagagcagt acactaggtt ccagcagtat 960  
ggggccgagg aatgcgtgtc gcaaattggg ggtgtgtgt gcccccgcc tggctgtgg 1020  
gctggactgc tacctgaaca gggccagagg aaagtccactt gcgaaggggg caacggccctg 1080  
ggctgcgggt ttgtttctg cccggactgt aaggaagcat accatgaagg ggattgcac 1140  
tcactgctcg aaccctcagg agccacttct caggcctaca gggtgaccaa aagagccgt 1200  
gagcaagctc gctgggagga ggcctccaag gaaaccatca agaagaccac caagccttgt 1260  
cctcgctgca acgtgccaat tgaaaaaaaaac ggaggatgtt tgcacatgaa gtgtcctcag 1320  
ccccagtgca agctggagtg gtgctggaaac tgcgtgtgt agtggaaaccg agcctgcattg 1380  
ggagatcaact ggtttgacgt ttagagagag atgcacttg gcccctggacg cacaacctca 1440  
agggaaactc cgaagattcc taccttcctt accattttct tcttctcgat gcatataagc 1500  
acataaatgc gcacacacaa acacaggctg cagattacag aagcagcccc tagatccctt 1560  
ctagggcacc cacagaaaaac cacagcaccc gctggccca gggggaggag gcactttcag 1620  
cctctggctc actcgaatgt cagagcttag atgagggtgc acctttgggt tggattctgt 1680  
agaagccatg agtgaggtgg gaagtgttt ccagggtgt tgccacgccc tggtaagta 1740  
acacctctgaa ggattctcag aagcacactt gagatctgag gaacgctgtc ttcacatgtat 1800  
aatcatctat tcccaaaggg ccccccgcag tagtcaaaac tatttggta tccccccaaa 1860  
tcctatctt acaaattggg ctgtgagat tacaacccct ctgtgtacta atcagcttat 1920  
caaccaagtg agaacctagg aaagctaatt ggatggcaga ctgtttaat cgccaggagg 1980  
actcagaagc caaacctact tccgttgcgt tcattatctg caactttttaga aagaaatgtat 2040  
cttttttcc ccctgaaaag ataacaagg ctgcaatttg gtttggagta ttcctactgc 2100  
agcctggaaag ttttagctca ctgtgaattt aacagagaaa gtgcctataa agggggcggt 2160  
tttaagagac aatcccatga tgctgcgcca atgctaacaa cagggtcaag aaacacaatg 2220  
tttatagaag gagcatccct cgaccatctg aatgagagta tgccctgaccc cttccaccac 2280  
aagtggggac acctctgcat atctgctccc tcctctgtgt ttaagccccca gggagccccca 2340  
tccacccagt ggtcctacag acagggcaat acacacacac caagatagcc ttcagatcaa 2400

|             |            |            |             |            |             |      |
|-------------|------------|------------|-------------|------------|-------------|------|
| catgcatcac  | actcaagtgt | taatcttca  | aggttttctt  | ttcttttcc  | tgttttttat  | 2460 |
| ttgttttgct  | tttgctttt  | ttttttttt  | ttttgggtgg  | ggggggcta  | ccaaacctga  | 2520 |
| ggcctagagc  | taaaaatcat | atagaatga  | tgttatctt   | tggtgtgagg | aaaggccagc  | 2580 |
| tggcctaagt  | tcacacattt | gtcccagtgg | cccttagactc | caccaggcca | gtctccaaaa  | 2640 |
| tgaaaagacc  | acctgtcaag | cagcagtcag | gagtctgtat  | tcaccatca  | ctatttttt   | 2700 |
| tccatcattt  | tgcttgcctc | tgcctccttc | cacacccgtt  | tgacgtaatc | gcattggaa   | 2760 |
| gccaggacaa  | tgttgctgt  | tctgcttgg  | gtaaagggac  | tccctgaagc | tctgtggctc  | 2820 |
| tccagtagtgg | tccctttcc  | ttcctaacag | atgcataatgt | tttcttcaga | atacaatagt  | 2880 |
| gattcttaaa  | ataacccaaa | agacaggcat | ccacagtgtt  | tgagcatgaa | tcacagcctg  | 2940 |
| cattgtgtga  | gtgtgaatag | tggataaaa  | gtggatgtca  | gaagagtgga | aatcaaacct  | 3000 |
| ctgcaaagca  | atctttctct | ttctgtgaag | tgttattaaga | aataccgtaa | gtctgtgtt   | 3060 |
| gtgggtgtac  | ccagactgtc | aatcaataaa | gacccagact  | gtcaatgaaa | aaaaaaaaaaa | 3120 |
| aaaaaaaaaa  | aaaaaaa    |            |             |            |             | 3136 |

<210> 11

<211> 3170

<212> DNA

<213> Mus musculus

<400> 11

tcacggcagg ggaagggggga ggaggcctgg atgactaaac ctgacagaaa cgctgggtgg 60  
aggctcgggc gggcgccagt gcccgcgtag gtccttctcg accccgagcc accaccgc 120  
cggtgaccat gatagtgttt gtcaggttca actccagcta tggctccca gtggaggtcg 180  
attctgacac cagcatctt cagctcaagg aagtggttgc taagcgacag ggggttccag 240  
ctgaccagct gcgtgtgatt ttgcgggga aggagcttcc gaatcacctg acggttcaaa 300  
actgtgacct ggaacaacag agtattgtac acatagtaca gagaccacgg aggagaagtc 360  
atgaaacaaa tgcatcttgg ggggacgaac cccagagcac ctcagaggc tccatatggg 420  
agtccaggag cttgacacga gtggacactga gcagccatac cctgccccgt gactctgtgg 480  
ggctggcggt cattctggac acagacagta agagggattc agaagcagcc agaggtccag 540  
ttaaacccac ctacaacagc ttttcatct actgcaaagg cccctgccc aaggtccagc 600  
ctggaaaagct ccgagttcag tgtggcacct gcaaacaagg aaccctcacc ttggcccaga 660  
atttttcttt aaatgtggag cacacccaac ctcagacaaag gacacgtcg tagctttgaa 720  
cctgatacc agcaacaggc gcagcatccc ttgcatagcg tgcacagatg tcaggagccc 780  
tgtcctggtc ttccagtgtc accaccgtca cgtatctgt ttggactgtt tccacttgta 840  
ttgtgtcaca agactcaacg atcggcagtt tgtccacgt gctcaacttg gctactccct 900  
gccgtgtgt a gctggctgtc ccaactccct gattaaagag ctccatcaact tcaggatcct 960  
tggagaagag cagtacacta ggtaccagca gtatggggcc gaggaatgcg tgctgcaaat 1020  
gggagggtgtg ctgtgcccc gtcctggctg tggagctgga ctgctacctg aacaggc 1080  
gaggaaagtc acctgcgaag ggggcaacgg cctgggctgc gggtttggg tctgccccgg 1140  
ctgtaggaa gcataccatg aaggggattt cgactcaactg ctcgaaccct caggagccac 1200  
ttctcaggcc tacaggggtgg acaaaagacg cgctgagcaa gtcgctggg aggaggccctc 1260  
caaggaaacc atcaagaaga ccaccaagcc ttgtcctcg tgcaacgtgc caattgaaaa 1320  
aaacggagga ttagtgcaca tgaagtgtcc tcagccccag tgcaagctgg a gttgtgtcg 1380  
gaactgtggc tttgagtgga accgagcctg catgggagat cactggttt acgtgttagag 1440  
agagatgtca ctggccctg gacgcacaac ctcaaggaa actccgaaga ttcctacatt 1500  
ccttagccat ttcttcttct cgatgcataat aagcacataa atgcgcacac acaaacacag 1560  
gctgcagatt acagaaggcag cccctagatc cttcttaggg caccacaga aaaccacagc 1620  
acccgctggc cccagggggga ggaggactt tcagcctctg gtcactcgat atgtcagagc 1680  
tttagatgagg gtgcacctt ggttggatt ctgttagaagc catgagttag gttggaaagt 1740  
ttttccaggg ttgttgccac gcccctggta agtaacacct ctgaggattc tcagaagcac 1800  
acttgagatc ttaggaacgc tgctctcatg tagtaatcat ctattccaa a gggccccct 1860  
gcagtagtca aaactatgg tttatcccc caaatctat ctttacaaat ggtgtgtat 1920  
agattacaac ccctctgtgt actaatcgc ttatcaacca agtgagaacc taggaaagct 1980  
aattggatgg cagactgttt aaatcgcagg gaggactcag aagccaaacc tacttccgtt 2040  
cgttcatta tctgcaactt tagaaagaaa tgatctttt ttccccctga aaagataaca 2100

aagtctgcaa tttgggttgg agtattccta ctgcagcctg gaagtttagc ttcaactgtga 2160  
 atttaacaga gaaagtgcct ataaaggggg cgtttttaag agacaatccc atgatgctgc 2220  
 gccaatgcta acaacagggt caagaaacac aatgtttata gaaggagcat ccctcgacca 2280  
 tctgaatgag agtatgcctg accccttcca ccacaagtgg ggacacctct gcatatctgc 2340  
 tcccttcctc gctgttaagc cccagggagc cccatccacc cagtggtcct acagacaggg 2400  
 caatacacac acaccaagat agccttcaga tcaacatgca tcacactcaa gtgttaatct 2460  
 ttcagggtt tctttctt ttctgttt ttatttgtt tgctttgt tttttttt 2520  
 ttttttttgg tgggtgtgg gctaccaaac ttgaggccta gagctaaaaa tcatatagaa 2580  
 atgatgttat cttgtgggt gaggaaaggc cagctggct aagttcacac tttgtccca 2640  
 gtggccctag actccaccca gccagctccc aaaataaaaa gaccacctgt caagcagcag 2700  
 tcaggagctt gatgtcaccc atcaactt ttttccatc attgtgttgc cctctgcctc 2760  
 cttccacacc cgtgtgacgt aatcgcatcg ggaagccagg acaatgtttg ctgttctgt 2820  
 ttggtaaag ggactccctg aagctctgt gctctccagt atggccctt ttccctccta 2880  
 acagatgcat atgtttctt cagaatacaa tagtgattct taaaataacc caaaagacag 2940  
 gcatccacag tgtgtgagca tgaatcacag cctgcattgt gtgagtgtga atagtggat 3000  
 aaaagtggat gtcagaagag tggaaatcaa acctctgaa agcaatctt ctcttctgt 3060  
 gaagtgtatt aagaaatacc tgaagtctgt gtgtgtggg gtacccagac tgtaaatcaa 3120  
 taaagaccca gactgtcaat gaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 3170

<210> 12  
 <211> 2918  
 <212> DNA  
 <213> Mus musculus

<400> 12  
 ctcagcgagg ggaaggggga ggaggcctgg atgactaaac ctgacagaaa cgctgggtgg 60  
 aggctcgggc gggcgccagt gccccgtcg gtccttctcg acccgagcc accacccgcc 120  
 cggtgccat gatagtgtt gtcagggtca actccagcta tggctccca gtggagggtcg 180  
 attctgacac cagcatctt cagctcaagg aagtgggtgc taagcgacag ggggttccag 240  
 ctgaccagct gcgtgtgatt tttgcccggg aggagcttcc gaatcacctg acggttcaaa 300  
 actgtgaccc ggaacaacag agtattgtac acatagtaca gagaccacgg aggagaagtc 360  
 atgaaacaaa tgcacatcgga ggggacgaa cccagagcac ctcagaggc tccatatggg 420  
 agtccaggag cttgacacga gtggacctga gcagccatac cctgcccgtg gactctgtgg 480  
 ggctggcggt cattctggac acagacagta agagggattc agaagcgcc agaggtccag 540  
 ttaaaccac ctacaacagc ttttcatct actgcaaagg cccctgcccac aaggtccagc 600  
 ctggaaagct ccgagttcag tggacacct gcaacaagc aaccctcacc ttggcccagc 660  
 tggctgtccc aactccctga ttaaagagct ccatcacttcc aggtacccctg gagaagagca 720  
 gtacacttagg taccoagcgt atggggccga ggaatgcgtg ctgcaaatgg gaggtgtgt 780  
 gtgccccctg cctggctgtg gagctggact gctacctgaa cagggccaga gaaagtcac 840  
 ctgcgaaggg ggcaacggcc tgggctgcgg gttgttttgc tgccggact gtaaggaagc 900  
 ataccatgaa ggggatttgc actcactgtc cgaaccctca ggagccactt ctcaggccta 960  
 cagggtgccac aaaagagccg ctgagcaagc tcgctggag gaggcctcca agggaaaccat 1020  
 caagaagacc accaaggctt gtcctcgctg caacgtgcca attaaaaaaa acggaggatg 1080  
 tatgcacatg aagtgtcctc agccccagtg caagctggag tggtgctgga actgtggctg 1140  
 tgagtggAAC cgagcctgca tggagatca ctggttgc gtgttagagag agatgtcact 1200  
 tggccctgga cgcacaacct caagggaaac tccgaagatt cctaccttcc tttagccattt 1260  
 cttcttctcg atgcatataa gcacataat ggcacacac aaacacaggc tgcagattac 1320  
 agaagcagcc cctagatct ttcttagggca cccacagaaa accacagcac cccgtggccc 1380  
 cagggggagg aggcacttcc agccctggc tcactcgaat gtcagagctt agatgagggt 1440  
 gcaccttggg tttggattct gtagaagcca tgagtggagtt gggaaagtgtt ttccagggtt 1500  
 gttgccacgc cctgggttaag taacaccttct gaggattctc agaagcacac ttgagatctg 1560  
 aggaacgcgtg ctctcatgtt gtaatcatct attcccaaag ggccccctgc agtagtcaaa 1620  
 actatgtt tatccccca aatcctatct ttacaaatgg tgctgtatgag attacaaccc 1680  
 ctctgtgtac taatcagctt atcaaccaag tgagaaccta ggaaagctaa ttggatggca 1740  
 gactgcttaa atcgcaggga ggactcagaa gccaaaccta cttccgttgc tttcattatc 1800

tgcaacttta gaaagaaaatg atctttttt cccctgaaa agataacaaa gtctgcaatt 1860  
tggtttggag tattcctact gcagcctgga agtttagctt cactgtaat ttaacagaga 1920  
aagtgcctat aaaggggcg ttttaagag acaatcccatt gatgctgcgc caatgcta 1980  
aacagggtca agaaacacaa tgtttataga aggagcatcc ctcgaccatc tgaatgagag 2040  
tatgcctgac cccttccacc acaagtgggg acacctctgc atatctgctc cctccctgc 2100  
tgttaagccc cagggagcccc catccaccca gtggcctac agacaggca atacacacac 2160  
accaagatag ccttcagatc aacatgcatc acactcaagt gttaatctt caaggtttc 2220  
tttctttt cctgtttttt atttgtttt ctttgtttt tttttttt tttttggtg 2280  
gtggtggggc tacccaaactt gaggcctaga gctaaaaatc atatagaaat gatgttatct 2340  
tgtggtgtga ggaaaggca gctggctaa gttcacactt ttgtcccagt ggcctagac 2400  
tccacccagc cagctccaa aatgaaaaga ccacctgtca agcagcagtc aggagtctga 2460  
tgtcaccat cactattttt tttccatcat tgtgcttgcc tctgcctcct tccacacccg 2520  
tgtgacgtaa tcgcattggg aagccaggac aatgtttgtt gttctgtttt gggtaaagg 2580  
actccctgaa gctctgtggc tctccagat ggtccctttt cttccctaaac agatgcata 2640  
gttttcttca gaataacaata gtgattctt aaataacccaa aagacaggc atccacagt 2700  
tgtgagcatg aatcacagcc tcgcattgtgt gagtgtgaat agtgggataa aagtggatgt 2760  
cagaagatg gaaatcaaac ctctgcaaag caatcttctt ctttctgtga agtgtattaa 2820  
gaaatacctg aagtctgtgt gtgtggtggt acccagactg tcaatcaata aagacccaga 2880  
ctgtcaatga aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2918

<210> 13

<211> 3043

<212> DNA

<213> Mus musculus

<400> 13

ctcagcgagg ggaaggggga ggaggcctgg atgactaaac ctgacagaaa cgctgggtgg 60  
aggctcgggc gggcgccagt gcccgcgtag gtccttctcg acccgcaagcc accacccgcc 120  
cggtgaccat gatagtgttt gtcaggttca actccagcta tggcttccca gtggaggtcg 180  
attctgacac cagcatctt cagctcaagg aagtgggtgc taagcgacag ggggttccag 240  
ctgaccagct gcgtgtgatt tttgcccggga aggagcttcc gaatcacctg acggttcaaa 300  
actgtgacct ggaacaacag agtattgtac acatagtaca gagaccacgg aggagaagtc 360  
atgaaacaaa tgcacatcgga ggggacgaac cccagagcac ctcagaggc tccatatggg 420  
agtccaggag cttgacacga gtggacctga gcagccatac cctgcccgtg gactctgtgg 480  
ggctggcggt cattctggac acagacagta agagggattc agaagcagcc agaggtccag 540  
ttaaaccac ctacaacagc ttttcatct actgcaaagg cccctgccac aaggtccagc 600  
ctggaaagct ccgagttcag tttggcacct gcaaaacaagc aaccctcacc ttggcccagg 660  
gcccatctt cttggacat gtccttaattt caaaccggat gagtggtgag tgccagtctc 720  
cagactgccc tggaaaccaga gctgaatttt tctttaaatg tggagcacac ccaacccatcag 780  
acaaggacac gtcggtagct ttgaacctga tcaccagcaa caggcgcagc atcccttgca 840  
tagcgtgcac agatgtcagg agccctgtcc tggcttccca gtgttaaccac cgtcacgtga 900  
tctgtttggc ctgttccac ttgtattgtc tcacaagact caacgatcgg cagtttgcc 960  
acgatgctca acttggctac tccctgcgt gtgtatgg ttttctgccc ggactgtaa 1020  
gaagcatacc atgaagggggaa ttgcgactca ctgctcgaaac cctcaggagc cacttctcag 1080  
gcctacaggg tggacaaaaag agccgctgag caagctcgct gggaggaggc ctccaaggaa 1140  
accatcaaga agaccaccaa gcctgtcct cgctgcaacg tgccaattga aaaaaacgg 1200  
ggatgtatgc acatgaagtgc tcctcagccc cagtgcaagc tggagtgggtg ctggaaactgt 1260  
ggctgtgagt ggaaccgagc ctgcattgggaa gatcactgtt ttgacgtgtaa gagagagatg 1320  
tcacttggcc ctggacgcac aacctcaagg gaaactccga agattccatc cttccttagc 1380  
catttcttct tctcgatgca tataagcaca taaatgcgca cacacaaaca caggctgcag 1440  
attacagaag cagcccttag atcctttctt gggcacccac agaaaaaccac agcaccggct 1500  
ggcccccagggg ggaggaggca ctttcagctt ctggctcaact cgaatgtcag agcttagatg 1560  
agggtgcacc tttggtttgg attctgtaga agccatgagt gaggtgggaa gtgtttcca 1620  
gggttggcacc caccggccctgg gtaagtaaca cctctgagga ttctcagaag cacacttgag 1680  
atctgaggaa cgctgcttc atgttagtaat catcttattcc caaaggcccc cctgcagtag 1740

tcaaaaactat ttgttatcc ccccaaatac tatcttaca aatggtgctg atgagattac 1800  
 aaccctctg tgtactaatac agcttatcaa ccaagtgaga acctaggaaa gctaatttga 1860  
 tggcagactg cttaatcgca agggaggact cagaagccaa acctacttcc gttcgatcc 1920  
 ttatctgcaaa cttagaaag aaatgatctt ttttcccccc tgaaaagata acaaagtctg 1980  
 caatttgggtt tggagtattc ctactgcagc ctggaaagttt agcttcactg tgaatttaac 2040  
 agagaaagtg cctataaagg gggcgaaaaa aagagacaat cccatgatgc tgcgcataatg 2100  
 ctaacaacag ggtcaagaaa cacaatgtt atagaaggag catcccctcga ccattctgaat 2160  
 gagagtatgc ctgaccctt ccaccacaag tggggacacc tctgcataatc tgctccctcc 2220  
 tctgctgtt agccccaggg agccccatcc acccagtggc cctacagaca gggcaataca 2280  
 cacacaccaa gatagccttc agatcaacat gcatcacact caagtgtta tcttcaagg 2340  
 ttttctttt ttttccctgt tttttattt ttttgcctttt gctttttttt tttttttttt 2400  
 tggtgggtt ggggctacca aacttgaggg ctagagctaa aaatcatata gaaatgatgt 2460  
 tatcttgtgg tggaggaaa ggccagctgg cctaagttca cactttgtc ccagtggccc 2520  
 tagactccac ccagccagct cccaaaatga aaagaccacc tgcagcagc cagtcaggag 2580  
 tctgatgtca cccatcacta tttttttcc atcattgtgc ttgcctctgc ctccttccac 2640  
 acccggtgtga cgtaatcgca ttgggaagcc aggacaatgt ttgctgttct gcttgggta 2700  
 aagggactcc ctgaagctt gtggctctcc agtatggtcc cttttccctt ctaacagatg 2760  
 catatgtttt ctccagaata caatagtgtat tcttaaaaata accccaaaaga caggcatcca 2820  
 cagtgtgtga gcatgaatca cagcctgcat tgggtgatgt tgaatagtgg gataaaaagtg 2880  
 gatgtcagaa gagtgaaat caaacctctg caaagcaatc ttctctttc tggtaagtgt 2940  
 attaagaat acctgaagtc tgggtgtgt gtggtacca gactgtcaat caataaagac 3000  
 ccagactgtc aatgaaaaaaaaaaaaaaaaaaa aaa 3043

<210> 14

<211> 3253

<212> DNA

<213> *Mus musculus*

<400> 14

ctcagcgagg ggaagggggga ggaggcctgg atgactaaac ctgacagaaa cgctgggtgg 60  
 aggctcgggc gggcgccagt gcccgcgtag gtccttctcg acccgccagcc accacccgccc 120  
 cggtaccat gatagtgtt gtcagggttca actccagcta tggctccca gtggagggtcg 180  
 attctgacac cagcatctt cagctcaagg aagtgggtgc taagcgacgg ggttccagct 240  
 gaccagctgc gtgtgattt tgccggaaag gagcttccga atcacctgac ggttccaaac 300  
 tggacctgg aacaacagag tattgtacac atagtacaga gaccacggag gagaagtcat 360  
 gaaacaaatg catctggagg ggacgaaccc cagagcacct cagagggtctc catatgggag 420  
 tccaggagct tgacacgagt ggacctgagc agccataccc tgccgggtgg ctctgtgggg 480  
 ctggcggtca ttctggacac agacagtaag aggattcag aagcagccag aggtccagtt 540  
 aaacccacct acaacagctt ttcatctac tgcaaaggcc cctgccacaa ggtccagcc 600  
 gggaaagctcc gagttcagtg tggcacctgc aaacaagcaa ccctcacctt ggcccaggcc 660  
 ccatcttgct gggacgtgt cttaatttca aaccggatga gtggtgatgt ccagtctcca 720  
 gactgcccgg gaaccagagc tgaatttttctt tttaaatgtg gagcacacccc aacccatcagac 780  
 aaggacacgt cggtagctt gaacctgatc accagcaaca ggccgcagcat cccttgcata 840  
 gcgtgcacag atgtcaggag ccctgtctcg gtctccagtt gtaaccaccc tcacgtgatc 900  
 tggggact gtttccactt gtattgtgtc acaagactca acgatggca gtttgcac 960  
 gatgctcaac ttggctactc cctgccgtgt gtagctggct gtcccaactc cctgattaaa 1020  
 gagctccatc acttcaggat ccttggagaa gagcagttaca ctaggtatcca gcagttatggg 1080  
 gccgaggaat gcgtgtgtca aatggggaggt gtgtgtgtcc cccgtctgg ctgtggagct 1140  
 ggactgctac ctgaacaggg ccagagggaaa gtccacctgcg aaggggccaa cggcctggcc 1200  
 tgggggtttt ttttctgccc ggactgttaag gaagcataacc atgaaggggaa ttgcactca 1260  
 ctgctcgaac cctcaggagc cacttctcag gcctacaggg tggacaaaag agccgcgtgag 1320  
 caagctcgct gggaggaggc ctccaaaggaa accatcaaga agaccaccaa gccttgcct 1380  
 cgctgcaacg tgccaattga aaaaaacgga ggatgtatgc acatgaagtg tcctcagccc 1440  
 cagtgcaacg tggagtgggtt ctggaaactgt ggctgtgtt ggaaccggagc ctgcattggga 1500  
 gatcactgggt ttgacgtgtt gggacgtgtt tcacttggcc ctggacgcac aacccatcaggg 1560

gaaactccga agattcctac cttccttagc catttcttct tctcgatgca tataaggaca 1620  
 taaatgcgca cacacaaca caggctgcag attacagaag cagccccatg atcctttcta 1680  
 gggcacccac agaaaaccac agcaccgcgt ggccccaggg ggaggaggca ctttcagcct 1740  
 ctggctcaact cgaatgtcag agcttagatg agggtgcacc ttgggttgg attctgtaga 1800  
 agccatgagt gaggtggaa gtgtttcca gggttgtgc cacgcccgtt gtaagtaaca 1860  
 cctctgagga ttctcagaag cacacttgag atctgaggaa cgctgctctc atgttagtaat 1920  
 catctattcc caaaggcccc cctgcagtag tcaaaaactat ttgtttatcc ccccaaatcc 1980  
 tatcttaca aatggtgctg atgagattac aaccctctg tgtactaatac agcttatcaa 2040  
 ccaagtgaga acctaggaaa gctaattgga tggcagactg cttaaatcgc agggaggact 2100  
 cagaagccaa acctacttcc gttcgttca ttatctgcaa cttagaaaag aaatgatctt 2160  
 ttttcccccc tgaaaagata acaaagtctg caatttgggt tggagtattc ctactgcagc 2220  
 ctggaagttt agcttcactg tgaatttaac agagaaagtg cctataaagg gggcggtttt 2280  
 aagagacaat cccatgatgc tgcgccaatg ctaacaacag ggtcaagaaa cacaatgttt 2340  
 atagaaggag catccctcga ccatctgaat gagagtatgc ctgaccctt ccaccacaag 2400  
 tggggacacc tctgcatatc tgctccctcc tctgctgtta agccccaggg agccccatcc 2460  
 acccagtggt cctacagaca gggcaataca cacacacca gatagccttc agatcaacat 2520  
 gcatcacact caagtgttaa tcttcagg ttttcttcc ttttcctgt ttttatttg 2580  
 ttttgccttt gctttttttt tttttttttt tgggtgggt ggggctacca aacttgaggc 2640  
 cttagagctaa aaatcatata gaaatgtatgt tatcttgggt tggaggaaa ggccagctgg 2700  
 cctaagttca cactttgtc ccagtgccc tagactccac ccagccagct cccaaaatga 2760  
 aaagaccacc tgtaaaggcag cagtcaggag tctgatgtca cccatcaacta tttttttcc 2820  
 atcattgtgc ttgcctctgc ctccctcc acccggtgtga cgtaatcgca ttgggaagcc 2880  
 aggacaatgt ttgcgtgttct gctttggta aaggactcc ctgaagctct gtggctctcc 2940  
 agtatggtcc ctttcccttc ctaacagatg catabttttt cttcagaata caatagtgtat 3000  
 tcttaaaaata accaaaaaga caggcatcca cagtggtgtga gcatgaatca cagcctgcatt 3060  
 tgggtgagtg tgaatagtgg gataaaaagtg gatgtcagaa gatggaaaat caaacctctg 3120  
 caaagcaatc tttctcttcc tggtaagtgt attaagaaaat acctgaagtc tgggtgtgtg 3180  
 gtggtaccca gactgtcaat caataaagac ccagactgtc aatgaaaaaaaaaaaaaaa 3240  
 aaaaaaaaaaaa aaa 3253

<210> 15  
 <211> 3254  
 <212> DNA  
 <213> Mus musculus

<400> 15

ctcagcgagg ggaagggggga ggaggccctgg atgactaaac ctgacagaaa cgctgggtgg 60  
 aggctcgggc gggcgccagt gccccgtag gtccttctcg acccgccagcc accacccgca 120  
 cggtaccat gatagtgttt gtcaggttca actccagcta tggctccca gtggaggctcg 180  
 attctgacac cagcatcttgc cagctcaagg aagtgggtgc taagcgacag ggggttccag 240  
 ctgaccagct gcgtgtgatt tttgccggga aggagcttcc gatcacctga cggttcaaaa 300  
 ctgtgacctg gaacaacaga gtattgtaca catagtacag agaccacggg ggagaagtca 360  
 tggaaacaaat gcatctggag gggacgaacc ccagagcacc tcagagggtct ccatatggga 420  
 gtccaggagc ttgacacggag tggacctgtc cagccatacc ctgcccgtgg actctgtggg 480  
 gctggcggtc attctggaca cagacagtaa gagggattca gaagcagcca gaggtccagt 540  
 taaaacccacc tacaacagct ttttcatcta ctgaaaggc ccctgcccaca aggtccagcc 600  
 tggaaagctc cgagttcagt gtggcacctg caaacaagca accctcacct tggcccaggg 660  
 cccatcttgc tgggacgtatg tcttaattcc aaacccggatg agtgggtgagt gccagtctcc 720  
 agactgcctt ggaaccagag ctgaattttt cttaaatgtt ggagcacacc caacctcaga 780  
 caaggacacg tcggtagct tgaacctgtat caccagcaac aggcgcagca tcccttgcatt 840  
 agcgtgcaca gatgtcagga gcccgttccct ggttccctcg tggtaaccacc gtcacgtgtat 900  
 ctgtttggac tggacttccact tggatgtgtt cacaagactc aacgatcggc agtttgcata 960  
 cgatgctcaa cttggctact ccctggcggt tggtagctggc tggcccaact ccctgattaa 1020  
 agagctccat cacttcagga tccttggaga agagcagtagc acttaggtacc agcagttatgg 1080  
 ggccgaggaa tgcgtgctgc aaatgggagg tggctgtgc ccccgctctg gctgtggagc 1140

tggactgcta cctgaacagg gccagaggaa agtcacctgc gaagggggca acggcctggg 1200  
 ctgcgggttt gtttctgcc gggactgtaa ggaagcatac catgaagggg attgcgactc 1260  
 actgctcgaa ccctcaggag ccacttctca ggcctacagg gtggacaaaa gagccgctga 1320  
 gcaagctcgc tgggaggagg cctccaagga aaccatcaag aagaccacca agccttgtcc 1380  
 tcgctgcaac gtgccaattg aaaaaaacgg aggatgtatg cacatgaagt gtcctcagcc 1440  
 ccagtgcaga ctggagtgg tctggaaactg tggctgttag tggaaccgag cctgcatggg 1500  
 agatcactgg tttgacgtgt agagagagat gtcacttggc cttggacgca caacctaag 1560  
 ggaaactcgg aagattccta ctttccttag ccatttctt tcctcgatgc atataagcac 1620  
 ataaaatgcgc acacacaac acaggctgca gattacagaa gcagccctta gatccttct 1680  
 agggcaccca cagaaaacca cagcaccggc tggcccccagg gggaggaggc actttcagcc 1740  
 tctggctcac tcgaatgtca gagcttagat gagggtgac ctttggttt gattctgttag 1800  
 aagccatgag tgaggtggg agtgtttcc agggttgtt ccacgcctg ggttaagtaac 1860  
 acctctgagg atttcagaa gcacacttga gatctgagga acgctgtct catgttagtaa 1920  
 tcatctattc ccaaaggcc cctgcagta gtcaaaaacta ttgttatac ccccaaatac 1980  
 ctatcttac aaatgggtct gatgagatta caacccctct gtgtactaat cagcttatca 2040  
 accaagttag aacctaggaa agctaattgg atggcagact gcttaaatcg cagggaggac 2100  
 tcagaagcca aacctacttc cgttcgttt attatctgca actttagaaa gaaatgtatc 2160  
 tttttcccc ctgaaaagat aacaaagtct gcaatttggt ttggagtatt cctactgcag 2220  
 ccttggaaaggtagt tagcttcact gtgaatttaa cagagaaaagt gcctataaaag gggcggttt 2280  
 taagagacaa tcccatgtat ctgcgccaat gctaacaaca gggtaagaa acacaatgtt 2340  
 tatagaagga gcatccctcg accatctgaa tgagagtatg cctgaccctt tccaccacaa 2400  
 gtggggacac ctctgcataat ctgctccctc ctctgctgtt aagccccagg gagccccatc 2460  
 cacccagtgg tcctacagac agggcaatac acacacacca agatagcctt cagatcaaca 2520  
 tgcacacac tcaagtgtta atcttcaag gttttttttt ctttttcctg ttttttattt 2580  
 gttttgcttt tgctttttt tttttttttt ttgggtggg tggggctacc aaacttgagg 2640  
 ccttagagcta aaaatcatat agaaatgtat ttatcttgcgtt gtgtgaggaa agggcagctg 2700  
 gcctaagtcc acactttgtt cccagtgcc cttagactcca cccagccagc tcccaaaaatg 2760  
 aaaagaccac ctgtcaagca gcagtcagga gtctgatgtc acccatcact atttttttc 2820  
 catcattgtg cttgcctctg cttcccttcca caccctgtt acgtaatcgc attgggaagc 2880  
 caggacaatg tttgctgttc tgctttgggt aaagggactc cctgaagctc tgtggctctc 2940  
 cagtatggtc cttttccctt cctaacagat gcatatgttt tcttcagaat acaatagtga 3000  
 ttcttaaaat aacccaaaag acaggcatcc acagtgtgt agcatgaatc acagcctgca 3060  
 ttgtgtgagt gtgaatagtg ggataaaaagt ggatgtcaga agagtggaaa tcaaaccctct 3120  
 gcaaagcaat ctttctctt ctgtgaagtg tattaagaaa tacctgaagt ctgtgtgtgt 3180  
 ggtggtaccc agactgtcaa tcaataaaga cccagactgt caatgaaaaa aaaaaaaaaa 3240  
 aaaaaaaaaa aaaa 3254

<210> 16  
 <211> 3253  
 <212> DNA  
 <213> Mus muculus

<400> 16

ctcagcgagg ggaaggggga ggaggcctgg atgactaaac ctgacagaaa cgctgggtgg 60  
 aggctcgggc gggcgccagt gccccgttag gtccttctcg acccgccagcc accacccggc 120  
 cggtgcacat gatagtgtt gtcaggttca actccagcta tggcttcca gtggaggctcg 180  
 attctgacac cagcatcttgc cagctcaagg aagtgggtgc taagcgacag ggggttccag 240  
 ctgaccagct gcgtgtgatt tttgcccgggaa aggagcttcc gaatcacctg acggttcaaa 300  
 actgtgaccc tggaaacacag agtattgtac acatagtaca gagaccacgg gagaagtcat 360  
 gaaacaaaatg catctggagg ggacgaaccc cagagcacct cagagggtctc catatggag 420  
 tccaggagct tgacacgagt ggacctgagc agccataaccc tgccgggtgg ctctgtgggg 480  
 ctggcggtca ttctggacac agacagtaag aggattcag aagcagccag aggtccagtt 540  
 aaacccaccc acaacagctt ttcatctac tgcaaaggcc cctgcccacaa ggtccagcc 600  
 gggaaagctcc gagttcagtg tggcacctgc aaacaagcaa ccctcacctt ggcccaggc 660  
 ccatctgtgtt gggacgttca aaccggatga gtggtgagt gtcacttccca 720

gactgccctg gaaccagagc tgaattttc tttaaatgtg gaggcacaccc aacctcagac 780  
 aaggacacgt cgtagctt gaacctgatc accagcaaca ggccgcagcat cccttcata 840  
 gcgtgcacag atgtcaggag ccctgtcctg gtcttccagt gtaaccaccc tcacgtgatc 900  
 tgtttgact gtttccactt gtattgttc acaagactca acgatcgca gtttgtccac 960  
 gatgctcaac ttggctactc cctgcccgtgt gtagctggct gtcccaactc cctgattaaa 1020  
 gagctccatc acttcaggat ccttggagaa gagcagttaca cttagttacca gcagttatggg 1080  
 gcccggaaat gctgtgtca aatggggaggt gtgtgtgcc cccgtccctgg ctgtggagct 1140  
 ggactgctac ctgaacaggaa ccagaggaaa gtcacctgctg aagggggcaa cggcctggc 1200  
 tgcgggtttg ttttctgccc ggactgttaag gaagcatacc atgaaggggaa ttgcactca 1260  
 ctgctcgaac cctcaggagc cacttctcag gcctacaggg tggacaaaag agccgctgag 1320  
 caagctcgct gggaggaggc ctccaaggaa accatcaaga agaccaccaa gccttgcct 1380  
 cgctgcaacg tgccaaattga aaaaaacggg ggtgttatgc acatgaagtgc tcctcagccc 1440  
 cagtgcacgc tggagtgggt ctggactgt ggctgtgagt ggaaccggc ctgcattggg 1500  
 gatcactgtt ttgacgtgtt gagagagatg tcacttggcc ctggacgcac aacctcaagg 1560  
 gaaactccga agattcctac cttccttagc catttcttct tctcgatgca tataaggcaca 1620  
 taaatgcgca cacacaaaca caggctgcag attacagaag cagccccctag atcctttcta 1680  
 gggcaccac agaaaaccac agcaccgcg gcccggggc ggaggaggca cttcagccct 1740  
 ctggctcaact cgaatgtcag agcttagatg agggtgcacc ttgggtttgg attctgtaga 1800  
 agccatgagt gaggtggaa gtgtttcca ggggttgc caccggctgg gtaagtaaca 1860  
 cctctgagga ttctcagaag cacacttgcg atctgaggaa cgctgctctc atgttagtaat 1920  
 catctattcc caaaggggccc cctgcagtag tcaaaactat ttgtttatcc ccccaaattcc 1980  
 tatctttaca aatgggtctg atgagattac aaccctctg tgtactaattc agcttataaa 2040  
 ccaagtgaga acctaggaaa gctaattgga tggcagactg cttaaatcgc agggaggact 2100  
 cagaagccaa acctacttcc gttcgttca ttatctgcaa ctttagaaaag aaatgatctt 2160  
 ttttcccccc taaaaagata acaaaagtctg caatttgggtt tggagtattc ctactgcagc 2220  
 ctggaggtt agcttcactg tgaatttaac agagaaaatg cctataaagg gggcggtttt 2280  
 aagagacaat cccatgtgc tgcccaatg ctaacaacag ggtcaagaaaa cacaatgttt 2340  
 atagaaggag catccctcga ccatctgaat gaggtatgc ctgaccctt ccaccacaag 2400  
 tggggacacc tctgcatatc tgctccctcc tctgctgtt agccccaggg agcccccattcc 2460  
 acccagtgtt cctacagaca gggcaataca cacacacca gatgccttc agatcaacat 2520  
 gcatcacact caagtgtttaa tcttcagg ttttcttcc ttttccctgt ttttatttg 2580  
 ttttgccttt gctttttttt tttttttttt tgggtgggtt ggggctacca aacttgaggc 2640  
 cttagactaa aaatcatata gaaatgtatg tattttgtgg ttttggggaaa ggccagctgg 2700  
 cctaagttca cactttgtc ccagtggccc tagactccac ccagccagct cccaaaatga 2760  
 aaagaccacc tgtaaaggcag cagtcaggag tctgatgtca cccatcaacta tttttttcc 2820  
 atcattgtgc ttgcctctgc ctccctccac acccggtgtga cgtaatcgca ttgggaagcc 2880  
 aggacaatgt ttgtgtttt gctttgggtt aaggactcc ctgaagctct gtggctctcc 2940  
 agtatggtcc ctcccttc ctaacagatg catatgttt cttcagaata caatagtgtat 3000  
 tcttaaaaata accccaaaaga caggcatcca cagttgtgtga gcatgaatca cagccctgcat 3060  
 tgtgtgagtg tgaatagtgg gataaaaatg gatgtcagaa gagttggaaat cccaaatctg 3120  
 caaagcaatc ttctcttcc ttttcccttc ttttcccttc ttttcccttc ttttcccttc 3180  
 gtggtaccca gactgtcaat caataaaagac ccagactgtc aatgaaaaaaaaaaaa 3240  
 aaaaaaaaaaaa aaa 3253

<210> 17  
 <211> 3092  
 <212> DNA  
 <213> Mus musculus

<400> 17  
 ctcagcgagg ggaaggggaa ggaggccctgg atgactaaac ctgacagaaa cgctgggtgg 60  
 aggctcgggc gggcccaagt gcccgcgtag gtccttctcg acccgccagcc accacccggcc 120  
 cggtgaccat gatagtaact gtgacccgtt gcaacagatg attgtacaca tagtacagag 180  
 accacggagg agaagtcatg aaacaaatgc atctgggggg gacgaacccc agagcaccc 240  
 agagggtcc atatgggagt ccaggagctt gacacgagtg gacccgtgca gccataccct 300

gccccgtggac tctgtggggc tggcggtcat tctggacaca gacagtaaga gggattcaga 360  
agcagccaga ggtccagttt aacccaccta caacagctt ttcatctact gcaaaggccc 420  
ctgccacaag gtccagcctg gaaagctccg agttcagtgt ggcacctgca aacaagcaac 480  
cctcacctg gcccaaggcc catcttgcgt ggacgatgtc ttaattccaa accggatgag 540  
tggtgagtgc cagttccag actgccctgg aaccagagct gaattttct ttaaatgtgg 600  
agcacaccca acctcagacca aggacacgtc ggtagcttg aacctgatca ccagcaacag 660  
gcccagcatc cttgcatacg cgtgcacaga tgtcaggagc cctgtccctgg tctccagtg 720  
taaccaccgt cacgtgatct gtttggactg tttccacttg tattgtgtca caagactcaa 780  
cgatcgccag tttgtccacg atgctcaact tggctactcc ctgcccgtgt tagctggctg 840  
tcccaactcc ctgattaaag agctccatca cttcaggatc cttggagaag agcagtacac 900  
taggtaccag cagtatgggg ccgaggaatg cgtgctgcaa atgggaggtg tgctgtgccc 960  
ccgtcctggc tgtggagctg gactgctacc tgaacaggcc cagaggaaag tcacctgcga 1020  
agggggcaac ggcctggct gcgggtttgt tttctgccc gactgttaagg aagcatacca 1080  
tgaagggat tgcaactcac tgctcgaaacc ctcaggagcc acttctcagg cctacagggt 1140  
ggacaaaaga gccgctgagc aagctcgctg ggaggaggcc tccaaggaaa ccatcaagaa 1200  
gaccaccaag ctttgcctc gctgcaacgt gccaattgaa aaaaacggag gatgtatgca 1260  
catgaagtgt cttcagcccc agtgcaagct ggagtggtgc tggaaactgtg gctgtgagtg 1320  
gaaccgagcc tgcatgggag atcaactggtt tgacgtgtag agagagatgt cacttggccc 1380  
tggacgcaca acctcaaggg aaactccgaa gattcctacc ttcccttagcc atttcttctt 1440  
ctcgatgcat ataagcacat aaatgcgcac acacaaacac aggctgcaaga ttacagaagc 1500  
ageccctaga tcctttctag ggcacccaca gaaaaccaca gcacccgtg gccccagggg 1560  
gaggaggcac tttcagcctc tggctcactc gaatgtcaga gcttagatga gggtgtcacct 1620  
ttggtttggaa ttctgttagaa gccatgagtg aggtggaaag tgttttccag ggttgttgc 1680  
acgcccctggg taagtaaacac ctctgaggat tctcagaagc acacttgaga tctgaggaac 1740  
gctgctctca tgttagtaatc atctattccc aaagggccccc ctgcagtagt caaaactatt 1800  
tgtttatccc cccaaatcct atctttacaa atggtgctga tgagattaca acccctctgt 1860  
gtactaatca gcttatcaac caagtgagaa cctaggaaag ctaattggat ggcagactgc 1920  
ttaaatcgca gggaggactc agaagccaaa cctacttccg ttgcgttcat tatctgcaac 1980  
tttagaaaga aatgatctt ttttccccct gaaaagataa caaagtctgc aatttggttt 2040  
ggagtattcc tactgcagcc tggaaagtta gcttcactgt gaatttaaca gagaaagtgc 2100  
ctataaaggg ggcgtttta agagacaatc ccatgatgtc ggcataatgc taacaacagg 2160  
gtcaagaaaac acaatgttta tagaaggagc atccctcgac catctgaatg agagtatgcc 2220  
tgacccttc caccacaagt ggggacacct ctgcataatct gtccttcct ctgctgttaa 2280  
gccccaggga gccccatcca cccagtggtc ctacagacag ggcaatacac acacaccaag 2340  
atagccttca gatcaacatg catcacactc aagtgttaat cttcaaggt ttcttttct 2400  
tttcctgtt ttttattgt tttgttttgc cttttttttt tttttttttt ggtgggtgg 2460  
gggctaccaa acttgaggcc tagagctaaa aatcatatag aaatgtatgtt atcttgggtt 2520  
gtgagggaaag gccagctggc ctaagttcac acttttgc cagtggccct agactccacc 2580  
cagccagetc ccaaaatgaa aagaccacct gtcaagcagc agtcaggagt ctgatgtcac 2640  
ccatcactat ttttttcca tcattgtgtc tgccctcgcc tccttcacca cccgtgtgac 2700  
gtaatcgcat tggaaagcca ggacaatgtt tgctgttctg ctttggtaa agggactccc 2760  
tgaagctctg tggctctcca gtatggtccc ttttccttcc taacagatgc atatgtttc 2820  
ttcagaatac aatagtgatt cttaaaataa cccaaaagac aggcattccac agtgtgtgag 2880  
catgaatcac agcctgcatt gtgtgaggtgt gaatagtggg ataaaagtgg atgtcagaag 2940  
agtggaaatc aaacctctgc aaagcaatct ttctctttct gtgaagtgta ttaagaaata 3000  
cctgaagtct gtgtgtgtgg tggtaaccag actgtcaatc aataaagacc cagactgtca 3060  
ataaaaaaaaaaaaaa aaaaaaaaaaa aa 3092

<210> 18

<211> 3255

<212> DNA

<213> Mus musculus

<400> 18

ctcagcgagg ggaaggggga ggaggcctgg atgactaaac ctgacagaaaa cgctggtggg 60



<210> 19  
<211> 3255  
<212> DNA  
<213> *Mus musculus*

<400> 19  
ctcagcgagg ggaaggggga ggaggcctgg atgactaaac ctgacagaaa cgctgggtggg 60  
aggctcgggc gggcgccagt gcccgcgtag gtccttctcg acccgagcc accaccgc 120  
cggtgaccat gatagtgtt gtcaggttca actccagta tggcttcca gtggaggtcg 180  
attctgacac cagcatctt cagctcaagg aagtgggtgc taagcgacag ggggttccag 240  
ctgaccagct gcgtgtgatt ttgccggga agagagttcc gaatcacctg acggttcaaa 300  
actgtgacct ggaacaacag agtattgtac acatagtaca gagaccacgg aggagaagtc 360  
atgaaacaaa tgcatcttga ggggacgaac cccagagcac ctcagggc tccatatggg 420  
agtccaggag cttgacacga gtggacactga gcagccatac cctgccccgt gactctgtgg 480  
ggctggcggt cattctggac acagacagta agagggattc agaagcagcc agaggtccag 540  
ttaaacccac ctacaacagc ttttcatct actgcaaagg cccctgccc aagggtccagc 600  
ctggaaagct ccgagttcag tgtggcacct gcaaacaagg aaccctcacc ttggcccagg 660  
gccccatctt cttggacgt gtcttaattc caaaccggat gagtggtag tgccagtctc 720  
cagactgccc tggaaaccaga gctgaattt tctttaaatg tggagcacac ccaacctcag 780  
acaaggacac gtcggtagct ttgaacctga tcaccagcaa caggcgcagc atcccttgc 840  
tagcgtgcac agatgtcagg agccctgtcc tggcttcca gtgttaaccac cgtcacgtga 900  
tctgttttga ctgtttccac ttgtattgtg tcacaagact caacgatcgg cagtttgtcc 960  
acgatgctca acttggctac tccctggcgt gttagctgg ctgtccaaac tccctgatta 1020  
aagagctcca tcacttcagg atccttggag aagagcagta cacttaggtac cagcagttatg 1080  
gggcccggagga atgcgtgtg caaatgggg gtgtgtgtg ccccccgtct ggctgtggag 1140  
ctggactgtc acctgaacag ggccagagga aagtccacgtc cgaaggggc aacggccttgg 1200  
gctgcggggtt tgggttctgc cgggactgtg aggaagcata ccatgaaggg gattgcact 1260  
caactgctcga accctcagga gccacttctc aggcctacag ggtggacaaa agagccgctg 1320  
agcaagctcg ctgggaggag gcctccaagg aaaccatcaa gaagaccaac aagccttgc 1380  
ctcgctgcaa cgtgccaatt gaaaaaaacg gaggatgtat gcacatgaag tgcctcagc 1440  
cccagtgcac gctggagtgg tgctgaaact gtggctgtg gtggaaaccga gcctgcattgg 1500  
gagatcaactg gttgacgtg tagagagaga tgcacttgg ccctggacgc acaacctcaa 1560  
gggaaactcc gaagatttcc accttcctt gccatttctt cttctcgatg catataagaca 1620  
cataaatgcg cacacacaaa cacaggctgc agattacaga agcagccct agatccttc 1680  
tagggcaccc acagaaaacc acagcacccg ctggccccag ggggaggagg cactttcagc 1740  
ctctggctca ctcaaatgtc agagctttaga tgagggtgca cttttgttt ggattctgta 1800  
gaagccatga gtgaggtggg aagtgtttc cagggttggt gccacccct ggtaagtaa 1860  
cacctctgag gattctcaga agcacactt agatctgagg aacgctgctc tcatgttaga 1920  
atcatctatt cccaaaggcc cccctgcagt agtcaaaact atttgtttat ccccccaat 1980  
cctatcttta caaatggtgc tgatgagatt acaacccctc tgcgtactaa tcaagtttac 2040  
aaccaagtga gaaccttagga aagctaattt gatggcagac tgcttaaatc gcagggaggaa 2100  
ctcagaagcc aaacctactt ccgttgcattt cattatctgc aacttttagaa agaaatgatc 2160  
ttttttccc cctgaaaaga taacaaagtc tgcaatttgg tttggagttat tcctactgca 2220  
gcctggaaagt ttagcttac tgcattttt acagagaaaatg tgcctataaa gggggcggtt 2280  
ttaagagaca atcccatgt gctgcgcac tgctaaacac aggtcaaga aacacaatgt 2340  
ttatagaagg agcatccctc gaccatctga atgagagtttgc gcctgacccc ttccaccac 2400  
agtggggaca cctctgcata tctgctccct cctctgtgt taagccccag ggagccccc 2460  
ccacccactg gtccatcaga cagggcaata cacacacacc aagatagcc tcaagatcaac 2520  
atgcattcaca ctcaagtgtt aatcttcaa gggtttctt tcttttccctt gttttttatt 2580  
tggtttgtt ttgtttttt tttttttttt tttgggtgggt gtggggctac caaactttag 2640  
gcctagagct aaaaatcata tagaaatgtt gttatcttgc ggtgtgagga aaggccagct 2700  
ggcctaagtt cacacttttgc tcccaacttgc cctagactcc acccagccag ctccccaaat 2760  
aaaaagacca cctgtcaagc agcagtcagg agtctgtatgtt caccatcac tattttttttt 2820  
ccatcattgt gcttgccttgc gcctcccttcc acacccgtgt gacgtaatcg cattgggaag 2880  
ccaggacaat gtttgcgtt ctgtttggg taaagggact ccctgaagct ctgtggctt 2940

ccagtatggc ccctttcct tcctaacaga tgcataatgtt ttcttcagaa tacaatagtg 3000  
attcttaaaa taacccaaaa gacaggcatc cacagtgtgt gagcatgaat cacagcctgc 3060  
attgtgtgag tgtaatagt gggataaaag tggatgttag aagagtggaa atcaaaccctc 3120  
tgcaaaagcaa tcttctctt tctgtgaagt gtattaagaa atacctgaag tctgtgtgt 3180  
tggtgttacc cagactgtca atcaataaaag acccagactg tcaatgaaaa aaaaaaaaaa 3240  
aaaaaaaaaa aaaaaa 3255

<210> 20  
<211> 3255  
<212> DNA  
<213> Mus musculus

<400> 20  
ctcagcgagg ggaaggggga ggaggcctgg atgactaaac ctgacagaaa cgctgggtgg 60  
aggctcgggc gggcgccagt gcccgcgtag gtccttctcg acccgcagcc accacccgcc 120  
cggtgaccat gatagtgttt gtcaggttca actccagcta tggcttccca gtggaggtcg 180  
attctgacac cagcatctt cagctcaagg aagtgggtgc taagcgacag ggggttccag 240  
ctgaccagct gcgtgtgatt tttgccggga aggagcttcc gaatcacctg acggttcaaa 300  
actgtgacct ggaacaacag agtattgtac acatagtaca gagaccacgg aggagaagtc 360  
atgaaacaaa tgcatcttga ggggacgaac cccagagcac ctcagagggc tccatatggg 420  
agtccaggag cttgacacga gtggacactg cagccatac cctgcccgtg gactctgtgg 480  
ggctggcggt cattctggac acagacagta agagggattc agaagcagcc agaggtccag 540  
ttaaaccac ctacaacacg ttttcatct actgcaaagg cccctgcac aaggtccagc 600  
ctggaaagct ccgagttcag tggcacctt gcaacaacgc aaccctcacc ttggcccagg 660  
gccccatctt cttggacat gtccttattt caaacccggat gagtgggtgag tgccagtc 720  
cagactgccc tggaaaccaga gctgaatttt tctttaaatg tggagcacac ccaacctcag 780  
acaaggacac gtcggtagct ttgaacctga tcaccagcaa caggcgcagc atcccttgca 840  
tagcgtgeac agatgtcagg agccctgtcc tggcttcca gtgttaaccac cgtcacgtga 900  
tctgttttggc ctgtttccac ttgtattgtt tcacaagact caacgatcgg cagtttgc 960  
acgatgctca acttggctac tccctgcgt gtgttagctgg ctgtcccaac tccctgatta 1020  
aagagctcca tcacttcagg atccttgag aagagcagta cactaggtac cagcagttat 1080  
ggggccgagga atgcgtgtc caaatggggat gtgtgtgtg ccccccgtt ggctgtggag 1140  
ctggactgtc acctgaacag gggccagagga aagtccaccc cgaagggggc aacggccctgg 1200  
gctgcgggtt tggcttctgc cgggactgta aggaagcata ccatgaaggg gattgcact 1260  
cactgctcga accctcagga gcccatttc aggcctacag ggtggacaaa agagccgctg 1320  
agcaagctcg ctgggaggag gccttccagg aaaccatcaa gaagaccacc aaccccttgc 1380  
ctcgctcgaat cgtgccaatt gaaaaaaaaacg gaggatgtat gcacatgaag tggcttcagc 1440  
cccagtgc当地 gctggagttt tgcttggact gtggctgtga gtagaaccga gctgc当地 1500  
gagatcaactg gtttgc当地 tagagagaga tgcacttgg ccctggacgc aacaccccaa 1560  
ggggaaactcc gaagatttcc accttccttta gccatttctt cttctcgatg catataagca 1620  
cataaaatgc当地 cacacacaaa cacaggctgc agattacaga agcagccctt agatcccttc 1680  
tagggcaccac acagaaaaacc acagcaccgg ctggccccag ggggaggagg cactttcagc 1740  
ctctggctca ctcgaatgtc agagcttgc tgagggtgca cttttgggtt ggattctgtt 1800  
gaagccatga gtgagggtggg aagtgtttc cagggttgc ggcacccctt gggtaagtt 1860  
cacctctgag gattctcaga agcacactt agatctgagg aacgctgtc tcatgttagt 1920  
atcatctatt cccaaaggcc cccctgc当地 agtcaaaact atttggttt ccccccaat 1980  
cctatcttta caaatgggtc tgatgagatt acaaccctt cttctcgatg catataagca 2040  
aaccacgtga gaacccatgg aagcttgc gatggcagac tgcttccatgc gcaggggagg 2100  
ctcagaagcc aaacctactt cccctgc当地 cattatctgc aacttttagaa agaaatgtc 2160  
ttttttccccc cctgaaaaaaa taacaaatgtc tgcaatttgg tttggaggat tccctactgca 2220  
gcctggaaatgt ttagcttccac tggatatttta acagagaaaag tgccttataaa gggggccctt 2280  
ttaagagagaca atcccatgt gctgc当地 tgc当地 aacccatgt agggtcaaga aacacaatgt 2340  
ttatagaagg agcatccctc gaccatctga atgagagat gctgc当地 ttccaccaca 2400  
agtggggaca cctctgc当地 tctgctccctt cccctgc当地 taagccccag ggagccccat 2460  
ccacccaggc gtccttccatgc caggc当地 aacccatgt aacccatgt tcaatgtc 2520

atgcatcaca ctcaagtgtt aatctttcaa ggaaaaatcc ttctttttttt cttttttctt gttttttatt 2580  
tggtttgcctt ttgcctttttt tttttttttt tttgggtggtg gtggggctac caaaactttag 2640  
gcctagagct aaaaatcata tagaaatgtat gttatcttgtt ggtgtgagga aaggccagct 2700  
ggcctaagtt cacacttttgc tcccagtggc cctagactcc acccagccag ctcccaaaat 2760  
gaaaagacca cctgtcaagc agcagtcagg agtctgtatgtt cacccatcac tattttttttt 2820  
ccatcattgtt gcttcctctt gccttccttcc acaccgtgtt gacgtaatcg cattgggaag 2880  
ccaggacaat gtttgcgtttt ctgcttttttgg taaaggact ccctgaagct ctgtggctct 2940  
ccagtatgtt cccttttcct tcctaacaga tgcatatgtt ttcttcagaa tacaatagtg 3000  
attcttaaaa taacccaaaaa gacaggcatc cacagtgtgtt gagcatgaat cacagcctgc 3060  
attgtgtgag tgtgaatagt gggataaaaag tggatgtcag aagagtggaa atcaaacctc 3120  
tgcaaagccaa tctttcttctt tctgtgaagt gtattaagaa atacctgaag tctgtgtgt 3180  
tgggtgttacc cagactgtca atcaataaaag acccagactg tcaatgaaaaa aaaaaaaaaa 3240  
aaaaaaaaaaa aaaaaa 3255

<210> 21  
<211> 105  
<212> PRT  
<213> Mus musculus

<400> 21  
Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
1 5 10 15  
Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
20 25 30  
Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
35 40 45  
Glu Leu Pro Asn His Leu Thr Val Gln Leu Asn Pro Pro Thr Thr Ala  
50 55 60  
Phe Ser Ser Thr Ala Lys Ala Pro Ala Thr Arg Ser Ser Leu Glu Ser  
65 70 75 80  
Ser Glu Phe Ser Val Ala Pro Ala Asn Lys Gln Pro Ser Pro Trp Pro  
85 90 95  
Arg Ala His Leu Ala Gly Thr Met Ser  
100 105

<210> 22  
<211> 344  
<212> PRT  
<213> Mus musculus

<400> 22  
Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
1 5 10 15  
Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
20 25 30  
Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
35 40 45  
Glu Leu Pro Asn His Leu Thr Val Gln Gly Pro Ser Cys Trp Asp Asp  
50 55 60  
Val Leu Ile Pro Asn Arg Met Ser Gly Glu Cys Gln Ser Pro Asp Cys  
65 70 75 80  
Pro Gly Thr Arg Ala Glu Phe Phe Lys Cys Gly Ala His Pro Thr  
85 90 95  
Ser Asp Lys Asp Thr Ser Val Ala Leu Asn Leu Ile Thr Ser Asn Arg

|   |     |     |
|---|-----|-----|
| 100   | 105 | 110 |
| Arg Ser Ile Pro Cys Ile Ala Cys Thr Asp Val Arg Ser Pro Val Leu |     |     |
| 115   | 120 | 125 |
| Val Phe Gln Cys Asn His Arg His Val Ile Cys Leu Asp Cys Phe His |     |     |
| 130   | 135 | 140 |
| Leu Tyr Cys Val Thr Arg Leu Asn Asp Arg Gln Phe Val His Asp Ala |     |     |
| 145   | 150 | 155 |
| Gln Leu Gly Tyr Ser Leu Pro Cys Val Ala Gly Cys Pro Asn Ser Leu |     |     |
| 165   | 170 | 175 |
| Ile Lys Glu Leu His His Phe Arg Ile Leu Gly Glu Gln Tyr Thr     |     |     |
| 180   | 185 | 190 |
| Arg Tyr Gln Gln Tyr Gly Ala Glu Glu Cys Val Leu Gln Met Gly Gly |     |     |
| 195   | 200 | 205 |
| Val Leu Cys Pro Arg Pro Gly Cys Gly Ala Gly Leu Leu Pro Glu Gln |     |     |
| 210   | 215 | 220 |
| Gly Gln Arg Lys Val Thr Cys Glu Gly Gly Asn Gly Leu Gly Cys Gly |     |     |
| 225   | 230 | 235 |
| Phe Val Phe Cys Arg Asp Cys Lys Glu Ala Tyr His Glu Gly Asp Cys |     |     |
| 245   | 250 | 255 |
| Asp Ser Leu Leu Glu Pro Ser Gly Ala Thr Ser Gln Ala Tyr Arg Val |     |     |
| 260   | 265 | 270 |
| Asp Lys Arg Ala Ala Glu Gln Ala Arg Trp Glu Glu Ala Ser Lys Glu |     |     |
| 275   | 280 | 285 |
| Thr Ile Lys Lys Thr Thr Lys Pro Cys Pro Arg Cys Asn Val Pro Ile |     |     |
| 290   | 295 | 300 |
| Glu Lys Asn Gly Gly Cys Met His Met Lys Cys Pro Gln Pro Gln Cys |     |     |
| 305   | 310 | 315 |
| Lys Leu Glu Trp Cys Trp Asn Cys Gly Cys Glu Trp Asn Arg Ala Cys |     |     |
| 325   | 330 | 335 |
| Met Gly Asp His Trp Phe Asp Val                                 |     |     |
| 340   |     |     |

<210> 23  
<211> 63  
<212> PRT  
<213> Mus musculus

<400> 23  
Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
1 5 10 15  
Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
20 25 30  
Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
35 40 45  
Glu Leu Pro Asn His Leu Thr Val Gln Leu Ala Val Pro Thr Pro  
50 55 60

<210> 24  
<211> 153  
<212> PRT  
<213> Mus musculus

<400> 24

Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
 1 5 10 15  
 Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
 20 25 30  
 Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
 35 40 45  
 Glu Leu Pro Asn His Leu Thr Val Gln Asn Cys Asp Leu Glu Gln Gln  
 50 55 60  
 Ser Ile Val His Ile Val Gln Arg Pro Arg Arg Arg Ser His Glu Thr  
 65 70 75 80  
 Asn Ala Ser Gly Gly Asp Glu Pro Gln Ser Thr Ser Glu Gly Ser Ile  
 85 90 95  
 Trp Glu Ser Arg Ser Leu Thr Arg Val Asp Leu Ser Ser His Thr Leu  
 100 105 110  
 Pro Val Asp Ser Val Gly Leu Ala Val Ile Leu Asp Thr Asp Ser Lys  
 115 120 125  
 Arg Asp Ser Glu Ala Ala Arg Gly Pro Gly Pro Ile Leu Leu Gly Arg  
 130 135 140  
 Cys Leu Asn Ser Lys Pro Asp Glu Trp  
 145 150

<210> 25  
 <211> 194  
 <212> PRT  
 <213> Mus musculus

<400> 25  
 Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
 1 5 10 15  
 Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
 20 25 30  
 Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
 35 40 45  
 Glu Leu Pro Asn His Leu Thr Val Gln Asn Cys Asp Leu Glu Gln Gln  
 50 55 60  
 Ser Ile Val His Ile Val Gln Arg Pro Arg Arg Arg Ser His Glu Thr  
 65 70 75 80  
 Asn Ala Ser Gly Gly Asp Glu Pro Gln Ser Thr Ser Glu Gly Ser Ile  
 85 90 95  
 Trp Glu Ser Arg Ser Leu Thr Arg Val Asp Leu Ser Ser His Thr Leu  
 100 105 110  
 Pro Val Asp Ser Val Gly Leu Ala Val Ile Leu Asp Thr Asp Ser Lys  
 115 120 125  
 Arg Asp Ser Glu Ala Ala Arg Gly Pro Val Lys Pro Thr Tyr Asn Ser  
 130 135 140  
 Phe Phe Ile Tyr Cys Lys Gly Pro Cys His Lys Val Gln Pro Gly Lys  
 145 150 155 160  
 Leu Arg Val Gln Cys Gly Thr Cys Lys Gln Ala Thr Leu Thr Leu Ala  
 165 170 175  
 Gln Asn Phe Ser Leu Asn Val Glu His Thr Gln Pro Gln Thr Arg Thr  
 180 185 190  
 Arg Arg

<210> 26  
<211> 183  
<212> PRT  
<213> Mus musculus

<400> 26  
Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
1 5 10 15  
Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
20 25 30  
Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
35 40 45  
Glu Leu Pro Asn His Leu Thr Val Gln Asn Cys Asp Leu Glu Gln Gln  
50 55 60  
Ser Ile Val His Ile Val Gln Arg Pro Arg Arg Arg Ser His Glu Thr  
65 70 75 80  
Asn Ala Ser Gly Gly Asp Glu Pro Gln Ser Thr Ser Glu Gly Ser Ile  
85 90 95  
Trp Glu Ser Arg Ser Leu Thr Arg Val Asp Leu Ser Ser His Thr Leu  
100 105 110  
Pro Val Asp Ser Val Gly Leu Ala Val Ile Leu Asp Thr Asp Ser Lys  
115 120 125  
Arg Asp Ser Glu Ala Ala Arg Gly Pro Val Lys Pro Thr Tyr Asn Ser  
130 135 140  
Phe Phe Ile Tyr Cys Lys Gly Pro Cys His Lys Val Gln Pro Gly Lys  
145 150 155 160  
Leu Arg Val Gln Cys Gly Thr Cys Lys Gln Ala Thr Leu Thr Leu Ala  
165 170 175  
Gln Leu Ala Val Pro Thr Pro  
180

<210> 27  
<211> 296  
<212> PRT  
<213> Mus musculus

<400> 27  
Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
1 5 10 15  
Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
20 25 30  
Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
35 40 45  
Glu Leu Pro Asn His Leu Thr Val Gln Asn Cys Asp Leu Glu Gln Gln  
50 55 60  
Ser Ile Val His Ile Val Gln Arg Pro Arg Arg Arg Ser His Glu Thr  
65 70 75 80  
Asn Ala Ser Gly Gly Asp Glu Pro Gln Ser Thr Ser Glu Gly Ser Ile  
85 90 95  
Trp Glu Ser Arg Ser Leu Thr Arg Val Asp Leu Ser Ser His Thr Leu  
100 105 110  
Pro Val Asp Ser Val Gly Leu Ala Val Ile Leu Asp Thr Asp Ser Lys  
115 120 125

Arg Asp Ser Glu Ala Ala Arg Gly Pro Val Lys Pro Thr Tyr Asn Ser  
 130 135 140  
 Phe Phe Ile Tyr Cys Lys Gly Pro Cys His Lys Val Gln Pro Gly Lys  
 145 150 155 160  
 Leu Arg Val Gln Cys Gly Thr Cys Lys Gln Ala Thr Leu Thr Leu Ala  
 165 170 175  
 Gln Gly Pro Ser Cys Trp Asp Asp Val Leu Ile Pro Asn Arg Met Ser  
 180 185 190  
 Gly Glu Cys Gln Ser Pro Asp Cys Pro Gly Thr Arg Ala Glu Phe Phe  
 195 200 205  
 Phe Lys Cys Gly Ala His Pro Thr Ser Asp Lys Asp Thr Ser Val Ala  
 210 215 220  
 Leu Asn Leu Ile Thr Ser Asn Arg Arg Ser Ile Pro Cys Ile Ala Cys  
 225 230 235 240  
 Thr Asp Val Arg Ser Pro Val Leu Val Phe Gln Cys Asn His Arg His  
 245 250 255  
 Val Ile Cys Leu Asp Cys Phe His Leu Tyr Cys Val Thr Arg Leu Asn  
 260 265 270  
 Asp Arg Gln Phe Val His Asp Ala Gln Leu Gly Tyr Ser Leu Pro Cys  
 275 280 285  
 Val Val Cys Phe Leu Pro Gly Leu  
 290 295

<210> 28  
 <211> 37  
 <212> PRT  
 <213> Mus musculus

<400> 28  
 Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
 1 5 10 15  
 Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
 20 25 30  
 Arg Arg Gly Ser Ser  
 35

<210> 29  
 <211> 53  
 <212> PRT  
 <213> Mus musculus

<400> 29  
 Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
 1 5 10 15  
 Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
 20 25 30  
 Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
 35 40 45  
 Glu Leu Pro Ile Thr  
 50

<210> 30

<211> 77  
 <212> PRT  
 <213> Mus musculus

<400> 30  
 Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
 1 5 10 15  
 Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
 20 25 30  
 Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
 35 40 45  
 Glu Leu Pro Asn His Leu Thr Val Gln Asn Cys Asp Leu Glu Gln Gln  
 50 55 60  
 Ser Ile Val His Ile Val Gln Arg Pro Arg Glu Lys Ser  
 65 70 75

<210> 31  
 <211> 14  
 <212> PRT  
 <213> Mus musculus

<400> 31  
 Met Ile Val Thr Val Thr Trp Asn Asn Arg Val Leu Tyr Thr  
 1 5 10

<210> 32  
 <211> 464  
 <212> PRT  
 <213> Mus musculus

<400> 32  
 Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
 1 5 10 15  
 Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
 20 25 30  
 Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
 35 40 45  
 Glu Leu Pro Asn His Leu Thr Val Gln Asn Cys Asp Leu Glu Gln Gln  
 50 55 60  
 Ser Ile Val His Ile Val Gln Arg Pro Arg Arg Ser His Glu Thr  
 65 70 75 80  
 Asn Ala Ser Gly Gly Asp Glu Pro Gln Ser Thr Ser Glu Gly Ser Ile  
 85 90 95  
 Trp Glu Ser Arg Ser Leu Thr Arg Val Asp Leu Ser Ser His Thr Leu  
 100 105 110  
 Pro Val Asp Ser Val Gly Leu Ala Val Ile Leu Asp Thr Asp Ser Lys  
 115 120 125  
 Arg Asp Ser Glu Ala Ala Arg Gly Pro Val Lys Pro Thr Tyr Asn Ser  
 130 135 140  
 Phe Phe Ile Tyr Cys Lys Gly Pro Cys His Lys Val Gln Pro Gly Asn  
 145 150 155 160  
 Leu Arg Val Gln Cys Gly Thr Cys Lys Gln Ala Thr Leu Thr Leu Ala  
 165 170 175

Gln Gly Pro Ser Cys Trp Asp Asp Val Leu Ile Pro Asn Arg Met Ser  
                  180                 185                 190  
 Gly Glu Cys Gln Ser Pro Asp Cys Pro Gly Thr Arg Ala Glu Phe Phe  
                  195                 200                 205  
 Phe Lys Cys Gly Ala His Pro Thr Ser Asp Lys Asp Thr Ser Val Ala  
                  210                 215                 220  
 Leu Asn Leu Ile Thr Ser Asn Arg Arg Ser Ile Pro Cys Ile Ala Cys  
                  225                 230                 235                 240  
 Thr Asp Val Arg Ser Pro Val Leu Val Phe Gln Cys Asn His Arg His  
                  245                 250                 255  
 Val Ile Cys Leu Asp Cys Phe His Leu Tyr Cys Val Thr Arg Leu Asn  
                  260                 265                 270  
 Asp Arg Gln Phe Val His Asp Ala Gln Leu Gly Tyr Ser Leu Pro Cys  
                  275                 280                 285  
 Val Ala Gly Cys Pro Asn Ser Leu Ile Lys Glu Leu His His Phe Arg  
                  290                 295                 300  
 Ile Leu Gly Glu Glu Gln Tyr Thr Arg Tyr Gln Gln Tyr Gly Ala Glu  
                  305                 310                 315                 320  
 Glu Cys Val Leu Gln Met Gly Gly Val Leu Cys Pro Arg Pro Gly Cys  
                  325                 330                 335  
 Gly Ala Gly Leu Leu Pro Glu Gln Gly Gln Arg Lys Val Thr Cys Glu  
                  340                 345                 350  
 Gly Gly Asn Gly Leu Gly Cys Gly Phe Val Phe Cys Arg Asp Cys Lys  
                  355                 360                 365  
 Glu Ala Tyr His Glu Gly Asp Cys Asp Ser Leu Leu Glu Pro Ser Gly  
                  370                 375                 380  
 Ala Thr Ser Gln Ala Tyr Arg Val Asp Lys Arg Ala Ala Glu Gln Ala  
                  385                 390                 395                 400  
 Arg Trp Glu Glu Ala Ser Lys Glu Thr Ile Lys Lys Thr Thr Lys Pro  
                  405                 410                 415  
 Cys Pro Arg Cys Asn Val Pro Ile Glu Lys Asn Gly Gly Cys Met His  
                  420                 425                 430  
 Met Lys Cys Pro Gln Pro Gln Cys Lys Leu Glu Trp Cys Trp Asn Cys  
                  435                 440                 445  
 Gly Cys Glu Trp Asn Arg Ala Cys Met Gly Asp His Trp Phe Asp Val  
                  450                 455                 460

<210> 33  
 <211> 464  
 <212> PRT  
 <213> Mus musculus

<400> 33  
 Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
       1                 5                 10                 15  
 Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
       20                 25                 30  
 Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
       35                 40                 45  
 Glu Leu Pro Asn His Leu Thr Val Gln Asn Cys Asp Leu Glu Gln Gln  
       50                 55                 60  
 Ser Ile Val His Ile Val Gln Arg Pro Arg Arg Arg Ser His Glu Thr  
       65                 70                 75                 80  
 Asn Ala Ser Gly Gly Asp Glu Pro Gln Ser Thr Ser Glu Gly Ser Ile

| 85  | 90  | 95  |
|---|-----|-----|
| Trp Glu Ser Arg Ser Leu Thr Arg Val Asp Leu Ser Ser His Thr Leu |     |     |
| 100   | 105 | 110 |
| Pro Val Asp Ser Val Gly Leu Ala Val Ile Leu Asp Thr Asp Ser Lys |     |     |
| 115   | 120 | 125 |
| Arg Asp Ser Glu Ala Ala Arg Gly Pro Val Lys Pro Thr Tyr Asn Ser |     |     |
| 130   | 135 | 140 |
| Phe Phe Ile Tyr Cys Lys Gly Pro Cys His Lys Val Gln Pro Gly Lys |     |     |
| 145   | 150 | 155 |
| Leu Arg Val Gln Cys Gly Thr Cys Lys Gln Ala Thr Leu Thr Leu Ala |     |     |
| 165   | 170 | 175 |
| Gln Gly Pro Ser Cys Trp Asp Asp Val Leu Ile Pro Asn Arg Met Ser |     |     |
| 180   | 185 | 190 |
| Gly Glu Cys Gln Ser Pro Asp Cys Pro Gly Thr Arg Ala Glu Phe Phe |     |     |
| 195   | 200 | 205 |
| Phe Lys Cys Gly Ala His Pro Thr Ser Asp Lys Asp Thr Ser Val Ala |     |     |
| 210   | 215 | 220 |
| Leu Asn Leu Ile Thr Ser Asn Arg Arg Ser Ile Pro Cys Ile Ala Cys |     |     |
| 225   | 230 | 235 |
| Thr Asp Val Arg Ser Pro Val Leu Val Phe Gln Cys Asn His Arg His |     |     |
| 245   | 250 | 255 |
| Val Ile Cys Leu Asp Cys Phe His Leu Tyr Cys Val Thr Arg Leu Asn |     |     |
| 260   | 265 | 270 |
| Asp Arg Gln Phe Val His Asp Ala Gln Leu Gly Tyr Ser Leu Pro Cys |     |     |
| 275   | 280 | 285 |
| Val Ala Gly Cys Pro Asn Ser Leu Ile Lys Glu Leu His His Phe Arg |     |     |
| 290   | 295 | 300 |
| Ile Leu Gly Glu Glu Gln Tyr Thr Arg Tyr Gln Gln Tyr Gly Ala Glu |     |     |
| 305   | 310 | 315 |
| Glu Cys Val Leu Gln Met Gly Gly Val Leu Cys Pro Arg Pro Gly Cys |     |     |
| 325   | 330 | 335 |
| Gly Ala Gly Leu Leu Pro Glu Gln Gly Gln Arg Lys Val Thr Cys Glu |     |     |
| 340   | 345 | 350 |
| Gly Gly Asn Gly Leu Gly Cys Gly Phe Val Phe Cys Arg Asp Cys Lys |     |     |
| 355   | 360 | 365 |
| Glu Ala Tyr His Glu Gly Asp Cys Asp Ser Leu Leu Glu Pro Ser Gly |     |     |
| 370   | 375 | 380 |
| Ala Thr Ser Gln Ala Tyr Arg Val Asp Lys Arg Ala Ala Glu Gln Ala |     |     |
| 385   | 390 | 395 |
| Arg Trp Glu Glu Ala Ser Lys Glu Thr Ile Lys Lys Thr Asn Lys Pro |     |     |
| 405   | 410 | 415 |
| Cys Pro Arg Cys Asn Val Pro Ile Glu Lys Asn Gly Gly Cys Met His |     |     |
| 420   | 425 | 430 |
| Met Lys Cys Pro Gln Pro Gln Cys Lys Leu Glu Trp Cys Trp Asn Cys |     |     |
| 435   | 440 | 445 |
| Gly Cys Glu Trp Asn Arg Ala Cys Met Gly Asp His Trp Phe Asp Val |     |     |
| 450   | 455 | 460 |

<210> 34  
<211> 451  
<212> PRT  
<213> Mus musculus

<400> 34

Met Ile Val Phe Val Arg Phe Asn Ser Ser Tyr Gly Phe Pro Val Glu  
 1 5 10 15  
 Val Asp Ser Asp Thr Ser Ile Leu Gln Leu Lys Glu Val Val Ala Lys  
 20 25 30  
 Arg Gln Gly Val Pro Ala Asp Gln Leu Arg Val Ile Phe Ala Gly Lys  
 35 40 45  
 Glu Leu Pro Asn His Leu Thr Val Gln Asn Cys Asp Leu Glu Gln Gln  
 50 55 60  
 Ser Ile Val His Ile Val Gln Arg Pro Arg Arg Arg Ser His Glu Thr  
 65 70 75 80  
 Asn Ala Ser Gly Gly Asp Glu Pro Gln Ser Thr Ser Glu Gly Ser Ile  
 85 90 95  
 Trp Glu Ser Arg Ser Leu Thr Arg Val Asp Leu Ser Ser His Thr Leu  
 100 105 110  
 Pro Val Asp Ser Val Gly Leu Ala Val Ile Leu Asp Thr Asp Ser Lys  
 115 120 125  
 Arg Asp Ser Glu Ala Ala Arg Gly Pro Val Lys Pro Thr Tyr Asn Ser  
 130 135 140  
 Phe Phe Ile Tyr Cys Lys Gly Pro Cys His Lys Val Gln Pro Gly Lys  
 145 150 155 160  
 Leu Arg Val Gln Cys Gly Thr Cys Lys Gln Ala Thr Leu Thr Leu Ala  
 165 170 175  
 Gln Gly Pro Ser Cys Trp Asp Asp Val Leu Ile Pro Asn Arg Met Ser  
 180 185 190  
 Gly Glu Cys Gln Ser Pro Asp Cys Pro Gly Thr Arg Ala Glu Phe Phe  
 195 200 205  
 Phe Lys Cys Gly Ala His Pro Thr Ser Asp Lys Asp Thr Ser Val Ala  
 210 215 220  
 Leu Asn Leu Ile Thr Ser Asn Arg Arg Ser Ile Pro Cys Ile Ala Cys  
 225 230 235 240  
 Thr Asp Val Arg Ser Pro Val Leu Val Phe Gln Cys Asn His Arg His  
 245 250 255  
 Val Ile Cys Leu Asp Cys Phe His Leu Tyr Cys Val Thr Arg Leu Asn  
 260 265 270  
 Asp Arg Gln Phe Val His Asp Ala Gln Leu Gly Tyr Ser Leu Pro Cys  
 275 280 285  
 Val Ala Gly Cys Pro Asn Ser Leu Ile Lys Glu Leu His His Phe Arg  
 290 295 300  
 Ile Leu Gly Glu Glu Gln Tyr Thr Arg Tyr Gln Gln Tyr Gly Ala Glu  
 305 310 315 320  
 Glu Cys Val Leu Gln Met Gly Gly Val Leu Cys Pro Arg Pro Gly Cys  
 325 330 335  
 Gly Ala Gly Leu Pro Glu Gln Gly Gln Arg Lys Val Thr Cys Glu  
 340 345 350  
 Gly Gly Asn Gly Leu Gly Cys Gly Phe Val Phe Cys Arg Asp Cys Lys  
 355 360 365  
 Glu Ala Tyr His Glu Gly Asp Cys Asp Ser Leu Leu Glu Pro Ser Gly  
 370 375 380  
 Ala Thr Ser Gln Ala Tyr Arg Val Asp Lys Arg Ala Ala Glu Gln Ala  
 385 390 395 400  
 Arg Trp Glu Glu Ala Ser Lys Glu Thr Ile Lys Lys Thr Thr Lys Pro  
 405 410 415  
 Cys Pro Arg Cys Asn Val Pro Ile Glu Lys Asn Gly Gly Cys Met His  
 420 425 430  
 Met Lys Cys Pro Gln Pro Gln Cys Lys Leu Glu Trp Cys Trp Asn Cys

435  
Gly Cys Glu  
450

440

445